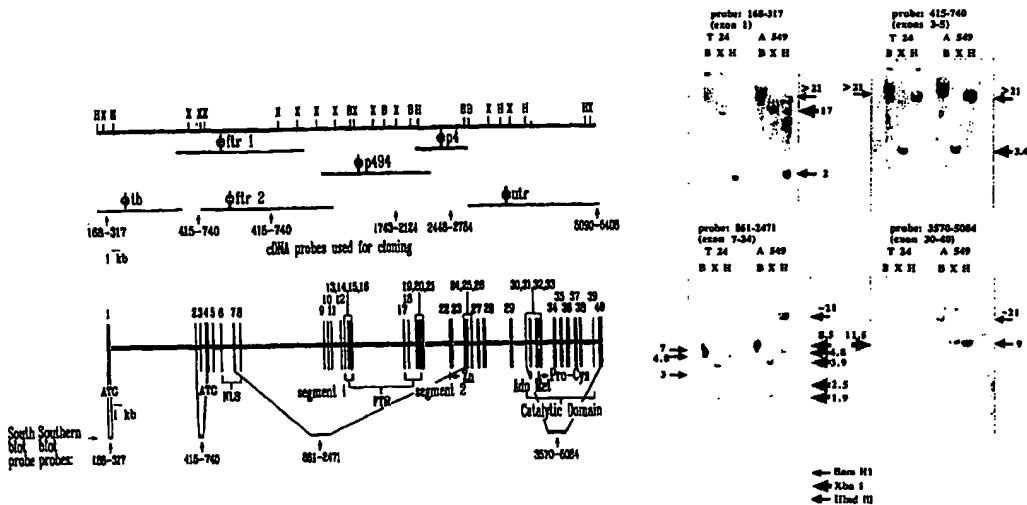




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(54) Title: DNA Methyltransferase Genomic Sequences and Antisense Oligonucleotides



(57) Abstract

The invention provides recombinant nucleic acids comprising nucleic acid sequences from the genomic DNA methyltransferase gene. The invention further provides sequence information for such nucleic acid sequences. In addition, the invention provides antisense oligonucleotides complementary to special regions of the genomic DNA methyltransferase gene or its RNA transcript. Finally, the invention provides methods for using such antisense oligonucleotides as analytical and diagnostic tools, as potentiators of transgenic plant and animal studies and gene therapy approaches, and as potential therapeutic agents.

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**DNA METHYLTRANSFERASE GENOMIC SEQUENCES
AND ANTISENSE OLIGONUCLEOTIDES**

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to modulation of gene expression. In particular, the invention relates to modulation of gene expression of the gene encoding DNA methyltransferase, and to modulation of gene expression that is regulated by the enzyme DNA methyltransferase.

Summary of the Related Art

Modulation of gene expression has become an increasingly important approach to understanding various cellular processes and their underlying biochemical pathways. Such understanding enriches scientific knowledge and helps lead to new discoveries of how aberrancies in such pathways can lead to serious disease states. Ultimately, such discoveries can lead to the development of effective therapeutic treatments for these diseases.

One type of cellular process that is of particular interest is how the cell regulates the expression of its genes. Aberrant gene expression appears to be responsible for a wide variety of inherited genetic disorders, and has also been implicated in numerous cancers and other diseases. Regulation of gene expression is a complex process, and many aspects of this process remain to be understood. One of the mysteries of this process resides in the fact that while the genetic information is the same in all tissues that constitute a multicellular organism, the expression of functions encoded by the genome varies significantly in different tissues.

In some cases, tissue-specific transcription factors are known to play a role in this phenomenon. (See Maniatis et al., *Science* 236: 1237-1245 (1987); Ingarham et al., *Annual Review of Physiology* 52: 773-791 (1990). However, several 5 important cases exist that cannot be readily explained by the action of transcription factors alone. For example, Midgeon, *Trends Genet.* 10: 230-235 (1994), teaches that X-inactivation involves the inactivation of an allele of a gene that resides on the inactive X-chromosome, while the allele on the active 10 X-chromosome continues to be expressed. In addition, Peterson and Sapienza, *Annu. Rev. Genet.* 27: 7-31 (1993), describes "parental imprinting", where an allele of a gene that is inherited from one parent is active and the other allele 15 inherited from the other parent is inactive. In both of these cases, both alleles exist in an environment containing the same transcription factors, yet one allele is expressed and the other is silent. Thus, something other than transcription factors must be involved in these phenomena.

Investigators have been probing what type of "epigenetic 20 information" may be involved in this additional control of the expression pattern of the genome. Holliday, *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 326: 329-338 (1990) discusses the possible role for DNA methylation in such epigenetic inheritance. DNA contains a set of modifications that is not 25 encoded in the genetic sequence, but is added covalently to DNA using a different enzymatic machinery. These modifications take the form of methylation at the 5 position of cytosine bases in CpG dinucleotides. Numerous studies have suggested that such methylation may well be involved in 30 regulating gene expression, but its precise role has remained elusive. For example, Lock et al., *Cell* 48: 39-46 (1987), raises questions about whether the timing of hypermethylation and X-inactivation is consistent with a causal role for 35 methylation. Similarly, Bartolomei et al., *Genes Dev.* 7: 1663-1673 (1993) and Brandeis et al., *EMBO J.* 12: 3669-3677 (1993), disclose timing/ causation questions for the role of methylation in parental imprinting.

Some of the shortcomings of existing studies of the role of DNA methylation in gene expression reside in the tools that are currently available for conducting the studies. Many studies have employed 5-azaC to inhibit DNA methylation.

5 However, 5-azaC is a nucleoside analog that has multiple effects on cellular mechanisms other than DNA methylation, thus making it difficult to interpret data obtained from these studies. Similarly, 5-azadC forms a mechanism based inhibitor upon integration into DNA, but it can cause trapping of DNA

10 methyltransferase (hereinafter, DNA MeTase) molecules on the DNA, resulting in toxicities that may obscure data interpretation.

More recently, Szyf et al., *J. Biol. Chem.* 267: 12831-12836 (1995), discloses a more promising approach using expression of antisense RNA complementary to the DNA MeTase gene to study the effect of methylation on cancer cells. Szyf and von Hofe, U.S. Patent No. 5,578,716, discloses the use of antisense oligonucleotides complementary to the DNA MeTase gene to inhibit tumorigenicity. These developments have provided powerful new tools for probing the role of methylation in numerous cellular processes. In addition, they have provided promising new approaches for developing therapeutic compounds that can modulate DNA methylation. One limitation to these approaches is that their effect is not immediate, due to the half life of DNA MeTase enzyme. Thus, although the expression of DNA MeTase is modulated, residual DNA MeTase enzyme can continue to methylate DNA until such residual enzyme is degraded. Polysome-associated DNA MeTase mRNA may also persist for some time, allowing additional translation to produce additional DNA MeTase enzyme. There is, therefore, a need for new antisense oligonucleotides which can act against intron regions of DNA MeTase RNA in the nucleus before its processing and association with polysomes. The development of such oligonucleotides will require obtaining sequence information about the non-coding regions of DNA MeTase RNA.

BRIEF SUMMARY OF THE INVENTION

The invention provides recombinant nucleic acids comprising nucleic acid sequences from the genomic DNA methyltransferase gene (DNA MeTase). The invention also 5 provides recombinant nucleic acids comprising nucleic acid sequences complementary to the genomic DNA MeTase gene. The invention further provides sequence information for such nucleic acid sequences. In addition, the invention provides 10 antisense oligonucleotides complementary to special target regions of the genomic DNA MeTase gene or its RNA transcript. Finally, the invention provides methods for using such 15 antisense oligonucleotides as analytical and diagnostic tools, as potentiators of transgenic plant and animal studies and for gene therapy approaches, and as potential therapeutic agents.

15 In a first aspect, the invention provides novel recombinant nucleic acid sequences comprising at least one nucleotide sequence selected from the nucleotide sequences of the genomic DNA MeTase gene. The sequence of the sense strand of the genomic DNA MeTase gene is shown in Figure 1. The 20 nucleotide sequence of the sense strand of the DNA MeTase gene is also set forth in the Sequence Listings as SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 14, SEQ ID NO 15, 25 SEQ ID NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, 30 SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO 38.

35 In a second aspect, the invention provides novel recombinant nucleic acid sequences complementary to at least one nucleotide sequence selected from the nucleotide sequences set forth in the Sequence Listings as SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID

NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11,
SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 14, SEQ ID NO 15, SEQ ID
NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20,
SEQ ID NO 21, SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID
5 NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29,
SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID
NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO
38.

10 In a third aspect, the invention provides antisense
oligonucleotides which inhibit the expression of DNA MeTase.
Such antisense oligonucleotides are complementary to a special
target region of RNA or double-stranded DNA that encodes DNA
MeTase. Preferably, such antisense oligonucleotides contain
one or more modified internucleoside linkage and may
15 optionally contain either deoxyribonucleosides,
ribonucleosides or 2'-O-substituted ribonucleosides, or any
combination thereof. Particularly preferred antisense
oligonucleotides according to this aspect of the invention
include chimeric oligonucleotides and hybrid oligonucleotides.

20 In a fourth aspect, the invention provides a method for
investigating the role of DNA MeTase in cellular growth,
including the growth of tumor cells. In the method according
to this aspect of the invention, the cell type of interest is
contacted with an antisense oligonucleotide according to the
25 invention, resulting in inhibition of expression of DNA MeTase
in the cell. The antisense oligonucleotides can be
administered at different points in the cell cycle, or in
conjunction with promoters or inhibitors of cell growth to
determine the role of DNA MeTase in the growth of the cell
30 type of interest.

35 In a fifth aspect, the invention provides methods for
inhibiting tumor growth comprising administering to a mammal,
including a human, antisense oligonucleotides according to the
invention. In the method according to this aspect of the
invention a therapeutically effective amount of an antisense

oligonucleotide according to the invention is administered for a therapeutically effective period of time to a mammal, including a human, which has tumor cells present in its body.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the nucleotide sequence for the sense strand of the DNA MeTase gene comprising the nucleotide acid sequences set forth in the Sequence Listings as SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 14, SEQ ID NO 15, SEQ ID NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO 38. Nucleotides in coding regions are identified as bold characters. Subscript numbers correspond to the DNA MeTase cDNA numbering of Yen et al. (Nucleic Acids Res. 9: 2287-2291 (1992) and Yoder et al. (J. Biol. Chem. 271: 31092-31097 (1996)). Preferred special target regions are underlined.

Figure 2 are representations of autoradiographs (panels A, B and D) and Western blots (panel C) in an experiment to identify complex formation between the oligonucleotides of the invention and DNA MeTase enzyme. Complex formation was reversed by boiling, and was independent of SAM.

Figure 3 is a graphic representation showing the ability of representative, nonlimiting, synthetic oligonucleotides of the invention to inhibit DNA MeTase activity in the nuclear extracts.

Figure 4 Panel (A) (Physical map and cloned genomic inserts of the human DNA MeTase gene) shows the restriction map and phage clones of the human DNA MeTase gene. The cDNA probes used for screening are indicated by arrows under the lines representing the genomic fragments contained in the phages (the name of each phage is indicated above the line) identified by each of

the probes. The numbers under the arrow indicate the 5' and 3' ends of the cDNA sequences included in each of the probes. The cDNA is numbered as in Yoder et al., 1996. Genomic inserts were isolated from the phages by NotI digestion and 5 sub-cloned into NotI linearized pBluescript SK+. Sub-clones were digested with restriction endonucleases (X = Xba 1, B = Bam H1, H = Hind III) Southern blotted and hybridized to exon specific ³²P labelled oligodeoxyribonucleotides or cDNA probes to produce a scale restriction map of the human DNA MeTase 10 gene.

Figure 4 Panel (B) is a schematic representation showing the exon-intron structure of the human DNA MeTase gene. Sub-clones shown in panel (A) were exon sequenced to determine exon-intron boundaries. Exons are depicted as 15 vertical bars and numbered above, introns as thick horizontal bars. Regions containing exons coding for specific function domains are depicted, NLS = nuclear localisation signal, FTR = replication foci targeting region, Zn = zinc binding domain, AdoMet Binding = S-adenosyl-methionine binding motif, Pro-Cys 20 = proline-cysteine catalytic motif, Catalytic Domain = region conserved in all CpG methyltransferases. Exonal location of proposed initiation codons = ATG.

Figure 4 Panel (C) shows the positions of exons determined by PCR analysis and verified by Southern blot 25 analysis. The fragments encoding the different segments of the human DNA MeTase mRNA were visualized by hybridization to the following cDNA probes: 1. A probe bearing the first exon. 2. A probe bearing exons 3-5 (starting spanning nucleotides 415-740 of the known cDNA) 3. A probe bearing 30 exons 7-20 4. A probe spanning exons 30-40. The cDNA probes are indicated under the map of the exon-intron structure, the dashed lines delineate the boundaries of exons spanned by each of the probes. The fragments visualized by each of the restriction enzymes are indicated by different shaded arrows. 35 The size of the visualized fragments is indicated next to the arrows. The size of the fragments visualized by each of the

probes corresponds to the size predicted by the restriction enzyme analysis of the genomic phages.

Figure 5 is a schematic representation showing the exon-intron boundaries of the human DNA MeTase gene and the exonic organization of the sequences corresponding to the known human mRNA (Yen et al., 1992; Yoder et al., 1996). The intron-exon boundaries were determined by exon sequencing of the genomic fragments described in figure 4 Panel (A). The intronic sequences flanking the boundaries are presented. Conserved splice acceptor (3' intron) and donor (5' intron) sites are depicted in bold. NLS = nuclear localisation signal (cDNA location : 817-874), FTR = replication foci targeting sequence (cDNA location : 1195-1938), Zn = zinc binding domain (cDNA location : 2194-2310), AdoMet = S-adenosyl-methionine binding motif (cDNA location : 3670-3687), Pro-Cys = proline-cysteine catalytic motif (cDNA location : 3910-3915 in domain IV), domain VI (cDNA location : 4003-4065), domain VIII (cDNA location : 4123-4197), domain IX (cDNA location : 4863-4935), domain X (cDNA location : 4948-5022) Catalytic Domain = region conserved in cytosine- 5 methyltransferases (cDNA location : 3649-5083). Numbering of the nucleotides of the human DNA MeTase cDNA is as in (Yoder et al., 1996).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention relates to modulation of gene expression. In particular, the invention relates to modulation of gene expression of the gene encoding DNA methyltransferase (DNA MeTase), and to modulation of gene expression that is regulated by the enzyme DNA MeTase. The patents and publications identified in this specification are within the knowledge of those skilled in this field and are hereby incorporated by reference in their entirety.

The invention provides recombinant nucleic acids comprising nucleic acid sequences from the genomic DNA MeTase gene. The invention further provides sequence information for such nucleic acid sequences. In addition, the invention provides antisense oligonucleotides complementary to regions of the genomic DNA MeTase gene or its RNA transcript which could not be targeted in the absence of such information. Finally, the invention provides methods for using such antisense oligonucleotides as analytical and diagnostic tools, as potentiators of transgenic plant and animal studies and gene therapy approaches, and as potential therapeutic agents.

In a first aspect, the invention provides novel recombinant nucleic acid sequences comprising at least one nucleotide sequence selected from the nucleotide sequences of the genomic DNA MeTase gene. The sequence of the sense strand of the genomic DNA MeTase is shown in Figure 1. Coding regions are identified as bold sequences.

In one preferred embodiment, the recombinant DNA molecule according to the invention comprises at least one nucleotide sequences selected from the nucleotide sequences shown in Figure 1 and corresponding to Sequence Listings SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 14, SEQ ID NO 15.

SEQ ID NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, 5 SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO. 38 in a replicatable vector. As used herein, the term "replicatable vector" designates a nucleic acid vector able to replicate in at least one cell type. Many such replicatable vectors are well known in the art (see e.g., 10 *Molecular Cloning*, 2d Edition, Cold Spring Harbor Laboratory Press (1989)).

In an additional preferred embodiment, the recombinant DNA molecule according to the invention comprises nucleotide sequences complementary to at least a portion of the 15 nucleotide sequence shown in Figure 1, and corresponding to at least one of the nucleotide sequences set forth as Sequence Listings SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ 20 ID NO 14, SEQ ID NO 15, SEQ ID NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, 25 SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO 38 in a replicatable vector.

In another preferred embodiment, the replicatable vector is an expression vector. The term "expression vector" refers, in one embodiment, to a replicatable vector able to support 30 the translation of part or all of its sequences into one or more peptides. The expression vector of this invention may replicate autonomously in the host cell, or may become integrated into the host cell DNA. The expression vector can be used to transform a host cell which is capable of 35 expressing the nucleotide sequence shown in Figure 1.

In yet another preferred embodiment, the term expression vector refers to a vector capable of supporting the transcription of part or all of its sequences into one or more transcripts. The vector according to this embodiment of the invention may replicate autonomously in the host cell, or may become integrated into the host cell DNA. The vector can be used to transform a host cell which is capable of transcription of the nucleotide sequence complementary to the nucleotide sequence shown in Figure 1. Preparation of recombinant DNA molecules and expression vectors and their use to transform host cells is well known in the art (see e.g., *Molecular Cloning*, 2d Edition, Cold Spring Harbor Laboratory Press (1989)).

In yet another embodiment, the invention also provides a host cell comprising recombinant DNA molecules according to the invention. According to this invention the term "host cell" refers to a cell which expresses the nucleotide sequences according to this invention.

This first aspect of the invention further provides a method for preparing DNA MeTase enzyme or a fragment thereof. The method according to this aspect of the invention comprises culturing a host cell in an appropriate culture media to express the nucleotide sequences according to the invention. Consequently, the host cell of the invention produces DNA MeTase enzyme or a fragment thereof, which may be conveniently separated from the host cell and the culture media by affinity binding, as described in detail in this specification. Fragments of DNA MeTase enzyme can then be used to produce antibodies specific for epitopes of DNA MeTase enzyme, according to standard immunological procedures. Such antibodies can be used to purify DNA MeTase enzyme, or to quantify it in conventional immunological assays.

In a second aspect, the invention provides a novel recombinant nucleic acid molecule comprising nucleic acid sequences complementary to at least part of the genomic DNA

MeTase gene. The sequence of the sense strand of the genomic DNA MeTase is shown in Figure 1. Coding regions are identified as bold sequences. For purposes of the invention, "complementary" means being sufficiently complementary to have the ability to hybridize to a genomic region, a gene, or an RNA transcript thereof under physiological conditions. Such hybridization is ordinarily the result of base-specific hydrogen bonding between complementary strands, preferably to form Watson-Crick or Hoogsteen base pairs, although other modes of hydrogen bonding, as well as base stacking can also lead to hybridization. As a practical matter, such complementarity can be inferred from the observation of specific DNA MeTase gene expression inhibition.

In one preferred embodiment, the recombinant DNA molecule according to the invention comprises nucleotide acid having a sequence complementary to at least part of the nucleotide sequences shown in Figure 1, and complementary to at least one of the nucleotide sequences set forth in the Sequence Listings as SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 14, SEQ ID NO 15, SEQ ID NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO 38 in a replicatable vector. In another preferred embodiment the replicatable vector is an expression vector. The replicatable vectors and expression vectors appropriate for this aspect of the invention are generally the same well known materials as discussed for the first aspect of the invention.

In yet another embodiment, the invention provides a host cell comprising recombinant DNA molecules according to the invention. This second aspect of the invention further provides a method for inhibiting DNA MeTase enzyme expression

in a transfected cell or transgenic animal. The method according to this aspect of the invention comprises culturing a host cell in an appropriate culture media to express the nucleotide sequences according to this aspect of the 5 invention. Consequently, the host cell of the invention produces decreased levels of DNA MeTase enzyme.

In a third aspect, the invention provides antisense oligonucleotides which inhibit the expression of DNA MeTase. Such antisense oligonucleotides are complementary to a special 10 target region of RNA or double-stranded DNA that encodes DNA MeTase.

The term "special target region" is used to denote sequences which could not be targeted without the sequence information provided by the invention. In particular, such 15 special target regions comprise a portion of the non-coding region of the nucleic acid shown in Figure 1. Most preferably, such special target region comprises from about 2 to about 50 nucleotides of such noncoding sequences. Such special target regions include, without limitation, intronic 20 sequences, untranslated 5' and 3' regions as well as intron-exon boundaries from the DNA methyltransferase gene. In certain embodiments, said target region may further comprise coding regions from the DNA MeTase gene.

Preferred non-limiting examples of antisense 25 oligonucleotides complementary to special target regions of RNA or double-stranded DNA encoding DNA MeTase according to the invention are shown in Table 1. Additional preferred oligonucleotides complementary to such special target regions have nucleotide sequences of from about 21 to about 35 30 nucleotides which include the nucleotide sequences shown in Table 1. Yet additional preferred oligonucleotides complementary to such special target regions have nucleotide sequences of from about 13 to about 19 nucleotides of the nucleotide sequences shown in Table 1.

TABLE 1

SEQ. ID NO.	SEQUENCE	TARGET (*)
5		
39	5' AGA ACT GAC TTA CCT CGG AT 3'	222
40	5' AGG GTG GGT CTG TGG GAG CA 3'	1039
41	5' CAG TAC ACA CTA GAC AGG AA 3'	1230
42	5' CAC ACT TAC AGG TGC TGA AG 3'	1441
10		
43	5' GAT CTC TTA CCT CGA TCT TG 3'	1593
44	5' CGC ATC CTT ACC TCT GTC CC 3'	1782
45	5' GGT GAG GTT ACC TCA CAG AC 3'	1968
46	5' GGC CTG ACC TAC CTC CGC TC 3'	2066
47	5' CCA AGG GTT ACC TTG ACG GC 3'	2214
15		
48	5' AAA GAT GCA AAC CTT GCT AG 3'	2330
49	5' TCC ATG CCT CCC TTG GGT AG 3'	2536
50	5' CCA GTG CTC ACT TGA ACT TG 3'	2669
51	5' ACA CAG AAT CTG AAG GAA AC 3'	2670
52	5' AGC TTG ATG CTG CAG AGA AG 3'	2844
20		
53	5' CAG GGG CAC CAC CTC GAG GA 3'	3258
54	5' CTT GCC CTT CCC TGG GGG AG 3'	3344
55	5' ACG GCC GCT CAC CTG CTT GG 3'	3473
56	5' TCC CGG CCT GTG GGG GAG AA 3'	3898
57	5' GGG CCA CCT ACC TGG TTA TG 3'	4064
25		
58	5' GGG TGC CAT TAC CTT ACA GA 3'	4242
59	5' ACA GGA CCC ACC TTC CAC GC 3'	4438
60	5' GCA CGC GGC CCT GGG GGA AA 3'	4606
61	5' GCC CCA CTG ACT GCC GGT GC 3'	4722
62	5' CCC GGG TGG TAT GCC GTG AG 3'	4809
30		
63	5' CTG CTC TTA CGC TTA GCC TC 3'	442
64	5' GAA GGT TCA GCT GTT TAA AG 3'	443
65	5' GTT TGG CAG GGC TGT CAC AC 3'	519

SEQ. ID NO.	SEQUENCE	TARGET (*)
66	5' CTG GCC CTA CCT GGT CTT TG 3'	597
67	5' CTA GCA ACT CTG TCA AGC AA 3'	633
68	5' TAG AGC TTT ACT TTT TCA TC 3'	717
69	5' GTT TGG GTG TTC TGT CAC AG 3'	753
70	5' GTT TGG CAG CTC TGC AGG GT 3'	876

For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-O-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamide, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleotide linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/ or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane. For purposes of the invention the term "2'-O-substituted" means substitution of the 2' position of the pentose moiety with an -O-lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an -O-aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be unsubstituted or may be substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy,

carboxyl, carbalkoxyl, or amino groups; or such 2' substitution may be with a hydroxy group (to produce a ribonucleoside), an amino or a halo group, but not with a 2'-H group.

5 Particularly preferred antisense oligonucleotides according to this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

10 For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred embodiment of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or 15 alkylphosphonothioate region. Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

20 For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred embodiment of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-O-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-O-substituted nucleotides, and a 25 deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide will contain at least three consecutive deoxyribonucleosides and will also contain ribonucleosides, 2'-O-substituted ribonucleosides, or combinations thereof.

30 The exact nucleotide sequence and chemical structure of an antisense oligonucleotide according to the invention can be varied, so long as the oligonucleotide retains its ability to inhibit DNA Metase expression. This is readily determined by testing whether the particular antisense oligonucleotide is active in a DNA Metase enzyme assay, a soft agar growth assay,

or an *in vivo* tumor growth assay, all of which are described in detail in this specification.

Antisense oligonucleotides according to the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (i.e., H-phosphonate chemistry for some cycles and phosphoramidite chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG). (See, e.g., Pon, *Methods in Molec. Biol.* 20: 465 (1993)).

Antisense oligonucleotides according to the invention are useful for a variety of purposes. For example, they can be used as "probes" of the physiological function of DNA MeTase by being used to inhibit the activity of DNA methyltransferase in an experimental cell culture or animal system and to evaluate the effect of inhibiting such DNA MeTase activity. This is accomplished by administering to a cell or an animal an antisense oligonucleotide according to the invention and observing any phenotypic effects. In this use, antisense oligonucleotides according to the invention are preferable to traditional "gene knockout" approaches because they are easier to use and can be used to inhibit DNA MeTase activity at selected stages of development or differentiation. Thus, antisense oligonucleotides according to the invention can serve as probes to test the role of DNA methylation in various stages of development.

Finally, antisense oligonucleotides according to the invention are useful in therapeutic approaches to benign and malignant tumors and other human diseases involving suppression of gene expression. The anti-tumor utility of antisense oligonucleotides according to the invention is described in detail elsewhere in this specification. In

addition, antisense oligonucleotides according to the invention may be used to activate silenced genes to provide a missing gene function and thus ameliorate disease symptoms. For example, the diseases beta thalassemia and sickle cell 5 anemia are caused by aberrant expression of the adult beta globin gene. Most individuals suffering from these diseases have normal copies of the fetal gene for beta globin. However, the fetal gene is hypermethylated and is silent. Activation of the fetal globin gene could provide the needed 10 globin function, thus ameliorating the disease symptoms.

For therapeutic use, antisense oligonucleotides according to the invention may optionally be formulated with any of the well known pharmaceutically acceptable carriers or diluents. This formulation may further contain one or more 15 DNA MeTase inhibitor and/or one or more additional anti-DNA MeTase antisense oligonucleotide or it may contain any other pharmacologically active agent.

In a fourth aspect, the invention provides a method for investigating the role of DNA MeTase in cellular growth, 20 including the growth of tumor cells. In the method according to this aspect of the invention, the cell type of interest is contacted with an antisense oligonucleotide according to the invention, resulting in inhibition of expression of DNA MeTase in the cell. The antisense oligonucleotides can be 25 administered at different points in the cell cycle, or in conjunction with promoters or inhibitors of cell growth to determine the role of DNA MeTase in the growth of the cell type of interest.

In a fifth aspect, the invention provides methods for 30 inhibiting tumor growth comprising administering to an animal, including a human, antisense oligonucleotides according to the invention. In the method according to this aspect of the invention a therapeutically effective amount of an antisense oligonucleotide according to the invention is administered for 35 a therapeutically effective period of time to an animal.

including a human, which has at least one tumor cell present in its body.

As used herein the term "tumor growth" is used to refer to the growth of a tumor cell. A "tumor cell" is a neoplastic cell. A tumor cell may be benign, i.e. one that does not form metastases and does not invade and destroy adjacent normal tissue, or malignant, i.e. one that invades surrounding tissues, is capable of producing metastases, may recur after attempted removal, and is likely to cause death of the host.

10 The terms "therapeutically effective amount" and "therapeutically effective period of time" are used to denote known treatments at dosages and for periods of time effective to reduce tumor cell growth. Preferably, such administration should be parenteral, oral, sublingual, transdermal, topical, 15 intranasal or intrarectal. When administered systemically, the therapeutic composition is preferably administered at a sufficient dosage to attain a blood level of antisense oligonucleotide from about 0.01 μ M to about 10 μ M. For localized administration, much lower concentrations than this 20 may be effective, and much higher concentrations may be tolerated. Preferably, a total dosage of DNA MeTase inhibitor will range from about 0.1 mg oligonucleotide per patient per day to about 200 mg oligonucleotide per kg body weight per day.

25 According to another embodiment, one or more of the oligonucleotides of the invention may be administered to an animal this aspect of the invention provides methods for inhibiting tumor growth comprising administering to an animal, including a human, more than one antisense oligonucleotide 30 according to the invention either sequentially or simultaneously in a therapeutically effective amount and for a therapeutically effective period of time.

The following examples are intended to further illustrate certain preferred embodiments of the invention and are not limiting in nature.

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Example 1Inhibition of DNA MeTase Expression As Measured in Nuclear Extracts Prepared from Human or Murine Cells

Nuclear extracts are prepared from 1×10^8 mid-log phase human H446 cells or mouse Y1 cells which have been grown under standard cell culture conditions. Cells were treated with medium supplemented with 1 mg/ml of an antisense oligonucleotide complementary to a noncoding region of the DNA MeTase RNA transcript or a randomer (negative control) oligonucleotide. The cells are harvested and washed twice with phosphate buffered saline (PBS), then the cell pellet is resuspended in 0.5 ml Buffer A (10 mM Tris pH 8.0, 1.5 mM MgCl₂, 5 mM KCl₂, 0.5 mM DTT, 0.5 mM PMSF and 0.5% Nonidet P40) to separate the nuclei from other cell components. The nuclei are pelleted by centrifugation in an Eppendorf microfuge at 2,000 RPM for 15 min at 4 °C. The nuclei are washed once in Buffer A and re-pelleted, then resuspended in 0.5 ml Buffer B (20 mM Tris pH 8.0, 0.25% glycerol, 1.5 mM MgCl₂, 0.5 mM PMSF, 0.2 mM EDTA 0.5 mM DTT and 0.4 mM NaCl). The resuspended nuclei are incubated on ice for 15 minutes then spun at 15,000 RPM to pellet nuclear debris. The nuclear extract in the supernatant is separated from the pellet and used for assays for DNA MeTase activity. For each assay, carried out in triplicate, 3 µg of nuclear extract is used in a reaction mixture containing 0.1 µg of a synthetic 33-base pair hemimethylated DNA molecule substrate with 0.5 µCi S-[methyl-³H] adenosyl-L-methionine (78.9 Ci/mmol) as the methyl donor in a buffer containing 20 mM Tris-HCl (pH 7.4), 10 mM EDTA, 25% glycerol, 0.2 mM PMSF, and 20 mM 2-mercaptoethanol. The reaction mixture is incubated for 1 hour at 37 °C to measure

the initial rate of the DNA MeTase. The reaction is stopped by adding 10% TCA to precipitate the DNA, then the samples are incubated at 4 °C for 1 hour and the TCA precipitates are washed through GFC filters (Fischer, Hampton, NH). Controls are DNA incubated in the reaction mixture in the absence of nuclear extract, and nuclear extract incubated in the reaction mixture in the absence of DNA. The filters are laid in scintillation vials containing 5 ml of scintillation cocktail and tritiated methyl groups incorporated into the DNA are counted in a β -scintillation counter according to standard methods. To measure inhibition of DNA MeTase expression, the specific activity of the nuclear extract from oligonucleotide-treated cells is compared with the specific activity of the extract from untreated cells. Treatment of cells with antisense oligonucleotides of the invention results in reduction in DNA MeTase activity in the nuclear extract.

Example 2

Antisense Oligonucleotide Accumulation in Cells

Antisense oligonucleotides are labeled with ^{32}P using standard procedures. 300,000 Y1 cells per well are plated in a six-well tissue culture plate. Labeled antisense oligonucleotides are added to a final concentration of 1 μM . Cells are harvested at different time points by trypsinization according to methods well known in the art, and washed extensively with PBS to remove nonincorporated compounds. The cell pellet is resuspended in 20 μl buffer RIPA (0.5% deoxycholic acid, 0.1% SDS, 1% NP-40, in PBS). The homogenate is incubated at 4 °C for 30 minutes, then spun in a microfuge at maximum speed for 30 minutes, after which the supernatant is transferred to a new tube. Two μl of supernatant are extracted with phenol-chloroform by adding 1 μl of phenol and 1 μl of chloroform, the suspension is mixed and the organic and aqueous phases are separated by centrifugation in a microfuge for 10 minutes at 15,000 RPM. The aqueous phase is extracted and loaded onto a 20% polyacrylamide-urea gel.

Visualization is by autoradiography. The results demonstrate that antisense oligonucleotides are taken up by the cells in a time-dependent manner.

Example 3

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Analysis of Cellular DNA Methylation in Cells

Treated with Antisense Oligonucleotides

Nuclear extracts are prepared from randomer oligonucleotide-treated cells and from antisense oligonucleotide-treated cells (1 μ M oligonucleotide) as described in Example 1. The DNA pellet is resuspended in 0.5 ml DNA extraction buffer (0.15 M NaCl, 1% SDS, 20 mM Tris-HCl pH 8.0, 5 mM EDTA), 100 μ g Proteinase K is added, and the suspension is incubated at 50 °C for 16 hours. The DNA is extracted in phenol-chloroform by adding 0.25 ml phenol and 0.25 ml chloroform. The suspension is mixed and the organic and aqueous phases are separated by centrifugation in a microfuge for 10 minutes at 15,000 RPM. One ml absolute ethanol is added to the aqueous phase and the DNA is precipitated by centrifugation in a microfuge for 15 minutes at 15,000 RPM. The DNA pellet is washed in 70% ethanol and re-pelleted by centrifugation. The DNA is resuspended in 100 μ l 20 mM Tris-HCl pH 8.0, 1 mM EDTA.

Two μ g DNA are incubated at 37 °C for 15 minutes with 0.1 unit of DNase, 2.5 μ l 32 P- α -dGTP (3000 Ci/mmol, Amersham, Cleveland, OH) and then 2 units Kornberg DNA Polymerase (Boehringer Mannheim, Mannheim, Germany) are added and the reaction mixture is incubated for an additional 25 minutes at 30 °C. Fifty μ l H₂O are then added and nonincorporated radioactivity is removed by spinning through a Microspin S-300 HR column (Pharmacia, Piscataway, NJ). Labelled DNA (20 μ l) is digested with 70 μ g micrococcal nuclease (Pharmacia, Piscataway, NJ) in the manufacturer's recommended buffer for 10 hours at 37°C. Equal amounts of radioactivity are loaded onto TLC phosphocellulose plates (Merck, Darmstadt, Germany) and the 3' mononucleotides are separated by chromatography in one direction, in 66:33:1 isobutyric acid/H₂O/NH₄OH. The

chromatograms are exposed to XAR film (Eastman Kodak, Rochester, NY) and the autoradiograms are scanned by laser densitometry (Scanalytics, CSPI, Billerica, MA). Spots corresponding to cytosine and 5-methylcytosine are quantified and the percentage of non-methylated CG dinucleotides is determined. The results are expected to demonstrate an overall reduction in the percentage of non-methylated CG dinucleotides in antisense oligonucleotide-treated cells, relative to randomer-treated cells.

To assess demethylation of specific genes, a procedure is carried out as generally described in J. Biol. Chem. 270: 12690-12696 (1995). Briefly, the genomic DNA (10 μ g) is extracted and subjected to digestion by 25 units HindIII, followed by digestion by either 25 units MspI (CG methylation insensitive) or 25 units HpaII (CG methylation sensitive) for 8 hours at 37°C. The digested DNA is separated on a 1.5% agarose gel and subjected to Southern blotting and hybridization with specific probes. The results are expected to show that genes which are ordinarily heavily methylated in the test cells become undermethylated, whereas the methylation levels for genes which are not ordinarily heavily methylated in the test cells are not significantly affected.

Example 4

25 Inhibition of Tumor Growth By Antisense Oligonucleotides

Y1 or H446 cells are plated on a 6 well plate at a density of 80,000 cells/well. Antisense oligonucleotide phosphorothioates complementary to a DNA MeTase noncoding region (about 0.5 to 20 μ M) are added to the cells. The cells are similarly treated daily for 7 days. Then, the cells are harvested and 3,000 live cells are plated in soft agar, for example, as described in Freedman and Shin, Cell 3: 355-359 (1974). Two weeks after plating, the number of colonies formed in soft agar are scored by visual examination. In the case of active antisense oligonucleotides, a dose-dependent reduction in the number of colonies is observed.

Alternatively, 6 to 8 week old LAF-1 mice (Jackson Labs, Bar Harbor, ME) are injected subcutaneously in the flank area with 2×10^6 Y1 cells. Three days later, the mice are injected with 1-5 mg/kg antisense oligonucleotide phosphorothioates complementary to a DNA MeTase noncoding region. This dosing is repeated every two days. After one month, the mice are sacrificed and the tumor size is determined according to standard protocols. (see e.g., Ramchandani et al. Proc. Natl. Acad. SCI. USA 94: 684-689 (1997) In the case of active antisense oligonucleotides, significant reduction in tumor size is observed, relative to controls treated with a randomized or a reverse antisense sequence.

Example 5

15 Affinity Binding of DNA MeTase Enzyme

To demonstrate affinity binding of DNA MeTase enzyme, a binding substrate hairpin oligonucleotide having the sequence 5'-CTGAAmCGGATmCGTTTCGATCUGTTCAAG-3' was provided at 4 μ M concentration. The hairpin oligonucleotide was labeled using polynucleotide kinase and gamma 32 P- γ -ATP (300 mCi/mmol, 50 μ Ci) (New England Biolabs, Beverly, MA) as recommended by the manufacturer. Labeled oligonucleotide was separated from nonincorporated radioactivity by passing through a G-50 Sephadex spin column (Pharmacia, Uppsala, Sweden). Labeled hairpin oligonucleotide (500 nM) was incubated with 5 μ g nuclear extract prepared as described in Example 1. The incubation, in the same buffer used for the DNA MeTase activity assay, was at 37 °C for 30 minutes. To determine whether complex formation was dependent on the cofactor SAM, the reaction was carried out both in the presence and the absence of SAM. Then, loading dye (0.3 M Tris-HCl pH 8.8, 0.2% SDS, 10% glycerol, 28 mM 2-mercaptoethanol and 24 μ g/ml bromophenol blue) was added and the sample was separated on a 5% SDS-polyacrylamide gel (SDS-PAGE) with a 4% stacking gel according to standard procedures. Following SDS-PAGE separation, the gel was exposed to autoradiography for

visualization of a complex migrating at 190 kDa. Alternatively, the gel was electrotransferred onto a PVDF membrane (Amersham Life Sciences, Buckinghamshire, England) using a electrotransfer apparatus (BioRad, Hercules, CA) at 5 250 milliamperes for 2.5 hours in electrotransfer buffer (3.03 g/l Tris base, 14.4 g/l glycine, 1 g/l SDS, pH 8.3) for Western blotting with a DNA MeTase-specific antisera. The membrane was blocked for 1 hour in a buffer containing 5 mM Tris base, 200 mM NaCl, 0.5% Tween-20 and 5% dry milk. Rabbit 10 antisera was raised according to standard procedures (see e.g., *Molecular Cloning*, 2d Edition, Cold Spring Harbor Laboratory Press (1989)) against a peptide sequence found in the catalytic domain of human and murine DNA MeTase (amino acids GQRLPQKGDVEMLKGGPPC). The antisera was added to the 15 membrane at a 1:200 dilution and incubated for 1 hour. The membrane was washed with the blocking buffer, then reacted with a 1:5000 dilution of goat anti-rabbit secondary antibody (Amersham, Cleveland, Ohio) for an additional hour. The membrane was then washed for 10 minutes in blocking buffer, 20 three times, and bands reacting with anti-DNA MeTase antibody were visualized using an ECL detection kit according to the manufacturer protocols (Amersham, Cleveland, Ohio).

The results demonstrated that a 190 kDa complex is detected by both autoradiography and Western blotting (see 25 FIG. 2), strongly indicating that the 190 kDa complex is formed between the hairpin oligonucleotide and DNA MeTase enzyme. Subsequent experiments using antisera raised against another peptide sequence found in the catalytic domain of human and murine DNA MeTase (amino acids GGPPCQGFSGMNRFSRTY 30 (see, Ramchandani et al. *supra*) confirmed the same results. These results further demonstrated that such complex formation is independent of the cofactor SAM since none was present. Furthermore, data showed that complex formation is achieved 35 within 30 minutes, thus suggesting that such complex formation provides an assay for the level of DNA MeTase in different cell samples and a method to purify methyltransferase by affinity binding.

Example 6Analysis of Treated Cells

Enzymatic activity profiles were performed to quantitate the ability of the synthetic oligonucleotides of the present invention to inhibit DNA methyltransferase expression. A549 cells (ATCC), and T24 cells (ATCC) were grown according to standard cell culture techniques. Cells were then treated for 24 hours with growth medium containing 250 nM of an antisense oligonucleotide complementary to a special target region of the DNA MeTase RNA transcript or a scrambled (negative control) oligonucleotide, and 10 μ g/ml lipofectin.

Cells were then harvested and washed twice with PBS and the nuclei were pelleted by centrifugation in an Eppendorf microfuge at 2,000 RPM for 15 min at 4 °C. The nuclei were washed once in Buffer A and re-pelleted, then resuspended in 0.5 ml Buffer B (20 mM Tris pH 8.0, 0.25% glycerol, 1.5 mM MgCl₂, 0.5 mM PMSF, 0.2 mM EDTA 0.5 mM DTT and 0.4 mM NaCl). The resuspended nuclei were incubated on ice for 15 minutes then spun at 15,000 RPM to pellet nuclear debris. The nuclear extract in the supernatant was separated from the pellet and used for assays for DNA MeTase activity. For each assay, carried out in triplicate, 3 μ g of nuclear extract was used in a reaction mixture containing 0.1 μ g of a synthetic 33-base pair hemimethylated DNA molecule substrate with 0.5 μ Ci S-[methyl-³H] adenosyl-L-methionine (78.9 Ci/mmol) as the methyl donor in a buffer containing 20 mM Tris-HCl (pH 7.4), 10 mM EDTA, 25% glycerol, 0.2 mM PMSF, and 20 mM 2-mercaptoethanol. The reaction mixture was incubated for 1 hour at 37 °C to measure the initial rate of the DNA MeTase. The reaction was stopped by adding 10% TCA to precipitate the DNA, then the samples were incubated at 4 °C for 1 hour and the TCA precipitates were washed through GFC filters (Fischer). Control were DNA samples incubated in the reaction mixture in the absence of nuclear extract, and nuclear extract incubated in the reaction mixture in the absence of DNA. The filters were laid in scintillation vials containing 5 ml of

scintillation cocktail and tritiated methyl groups incorporated into the DNA are counted in a β -scintillation counter according to standard methods. To normalize and thus compare specific activity of the nuclear extracts from cells 5 treated with various synthetic oligonucleotide both DNA MeTase and G3PDH activity were measured. FIG. 3 shows DNA MeTase enzymatic activity observed in A549 cells treated with 26 different synthetic oligonucleotides as indicated. Similar results were observed when using T24 cells. Note that values 10 were expressed as a percentage of activity observed in cells treated with scrambled synthetic oligonucleotides. The results show that the treatment of cells with antisense oligonucleotides of the invention results in reduction in DNA MeTase activity in the nuclear extracts.

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Example 7

Inhibition of Tumor Growth in Vivo

Ten to twelve week old female BALB/c nude mice (Taconic Labs, Great Barrington, NY) were injected subcutaneously in 20 the flank area with 2×10^6 preconditioned A549 human lung carcinoma cells. Preconditioning of these cells was done by a minimum of three consecutive tumor transplantations in the same strain of nude mice. Subsequently, tumor fragments of approximately 25 mgs were excised and implanted subcutaneously 25 in mice, in the left flank area under Forene anesthesia (Abbott Labs., Geneva, Switzerland). When the tumors reached a mean volume of 100 mm³, the mice were treated intravenously, by daily bolous infusion into the tail vein, with oligonucleotide saline preparations containing 2 mg/Kg of oligonucleotide 30 according to the present invention. The optimal final concentration of the oligonucleotide is established by dose response experiments according to standard protocols. Tumor volume was calculated according to standard methods every second day post infusion. (e.g., Meyer et al. Int. J. Cancer 35 43:851-856 (1989)). Treatment with the oligonucleotides of the invention caused a significant reduction in tumor weight

and volume relative to controls treated with randomized or reverse antisense sequence (data not shown). In addition, the activity of DNA MeTase enzyme was measured and found to be significantly reduced relative to randomer treated controls.

5 These results show that the oligonucleotides according to the invention are capable of inhibiting MeTase enzymatic activity and tumor growth.

Example 8

10 DNA MeTase Gene Organization and Structure

Information regarding the chromosomal organization of the human DNA MeTase gene is useful for (a) a comprehensive analysis of the mechanisms that underlie the regulation of DNA MeTase expression in oncogenic progression and developmental processes (e.g., analysis of potential alternative splicing products, regulatory elements such as enhancers and promoters reside in intronic genomic regions), and (b) for designing antisense oligodeoxyribonucleotides according to the invention. In order to obtain overlapping DNA fragments spanning the entire human DNA MeTase gene, several cDNA fragments spanning the known human DNA MeTase cDNA were generated via RT-PCR (mRNA source Hela and A549 cells) (Fig. 4A) and used as probes to screen human genomic DNA libraries from lung and placenta, in Lambda FIX II (Stratagene). The cDNA probes spanned the entire known human cDNA sequence (Yen et al., 1992 and Yoder et al., 1996). Genomic inserts were isolated from the phages by NotI digestion and sub-cloned into NotI linearized pBluescript SK+. Sub-clones were digested with restriction endonucleases (X = Xba 1, B = Bam H1, H = Hind III) Southern blotted and hybridized to exon specific ³²P labelled oligodeoxyribonucleotides or cDNA probes to produce a scale restriction map of the human DNA MeTase gene. Sub-clones were exon sequenced to determine exon-intron boundaries. Intron sizes were determined by either DNA sequencing (for introns less than 150 bp), PCR using 5' and 3' flanking exon sequences as primer sources (for introns less

than 2Kb) and restriction enzyme-Southern blot analysis using the enzymes indicated in A (data not shown) using oligonucleotides for each specific exon to verify the restriction enzyme. For larger introns (>2kb), the distance 5 between the exons was estimated by restriction enzyme analysis of phage insert and mapping the exons to the different restriction fragments using exon specific oligonucleotide probes (see physical map in figure 4A). The physical map obtained by restriction enzyme analysis of phage DNA (Fig. 4A) 10 was verified by a restriction enzyme-Southern blot analysis of human genomic DNA. Genomic DNA was prepared as described previously (Sambrook et al. 1989) from human lung carcinoma A549 cells (ATCC: CCL-185) and human bladder carcinoma cells: T24 (ATCC: HTB-4) and digested with restriction endonucleases 15 Xba 1 (X), Bam H1 (B), or Hind III (H), electrophoresed on a 1.5% agarose gel and Southern blotted. The fragments encoding the different segments of the human DNA MeTase mRNA were visualized by hybridization to the following cDNA probes: 1. A probe bearing the first exon. 2. A probe bearing exons 3-5 (starting spanning nucleotides 415-740 of the known cDNA) 3. A 20 probe bearing exons 7-20 4. A probe spanning exons 30-40. The cDNA probes are indicated under the map of the exon-intron structure, the dashed lines delineate the boundaries of exons spanned by each of the probes. The fragments visualized by 25 each of the restriction enzymes are indicated by different shaded arrows. The size of the visualized fragments is indicated next to the arrows. The size of the fragments visualized by each of the probes corresponds to the size predicted by the restriction enzyme analysis of the genomic 30 phages. The fragments predicted by the physical map of the different phages (Fig. 4A) were visualized with the cDNA probes in the Southern blots of genomic DNA (Fig. 4C, arrows 35 indicate the restriction enzyme fragments, and their sizes, visualized with each cDNA probe). The positions of exons determined by PCR analysis were verified by Southern blot analysis. The following primers were used to map by PCR the relevant intron boundaries and sizes: exons 4 to 5 : sense : 40

5' -aaaacgggaaccaagcaagaa ; antisense : 5' -tgagatgtgatggggttt ;
exons 5 to 6 : sense : 5' -ctgaacttcacctagcccc ; antisense :
gatggactcatccgattgg ; exons 6 to 7 : sense :
5' -ccctgccaaacggaaacctc ; antisense : 5' -gttctctggatgttaactcta
5 ; exons 7 to 8 : sense : agacgttagagttacatccag ; antisense :
5' -gctcttcaggttcttctgc ; exons 9 to 10 : sense :
5' -aagaaaagagactccgaagt ; antisense : tttctcgctccatcttcgt ;
exons 10 to 11 : sense : 5' -gtcagcccttaggagctgtt ; antisense :
5' -ggaaacagctatgaccatg (M13 reverse primer) ; exons 11 to 12 :
10 sense : 5' -gatgagaagaagcacagaag ; antisense :
5' -tcatcctcgcttttcatcagaa ; exons 12 to 13 : sense :
5' -ttctgatgaaaaagacgaggatga ; antisense :
5' -cattaccatctgcggat ; exons 13 to 14 : sense :
5' -aggagaagagacgcaaaacg ; antisense : 5' -agttcatgactgtttggcg
15 ; exons 17 to 18 : sense : 5' -gtactgtaagcacggtcacc ; antisense :
5' -aggtgctgaagccgatgagg ; exons 18 to 19 : sense :
5' -tggatcaactggcttgatgg ; antisense : 5' -ctcgatctgttgcaggat
; exons 21 to 22 : sense : 5' -aggcgagcccaggcgaggcg ; antisense :
5' -cgctctggcaagcctgcttg ; exons 22 to 23 : sense :
20 5' -gtgtcagcagcctgagtgt ; antisense : 5' -ctccgacccaagagatgcga
; exons 23 to 24 : sense : gtcccaatatggccatgaag ; antisense :
5' -gctagatacagcgggtttgagg ; exons 24 to 25 : sense :
5' -cgtcaagactgtatggaaagaagagt ; antisense :
5' -ctccatggcccagtttcgg ; exons 25 to 26 : sense :
25 5' -gtcacggcgctgtgggagga ; antisense : 5' -ttgaacttgttgcctctgt
; exons 26 to 27 : sense : 5' -gacctacttctaccagctgt ; antisense :
5' -ttgaacgtgaaggcctcagg ; exons 27 to 28 : sense :
5' -ctctactactcagccaccaa ; antisense : 5' -tagaacttgcgttgcacccgga ;
exons 28 to 29 : sense : 5' -tgagactgacataaaaatcc ; antisense :
30 5' -cgaggaagttagaagcggtg ; exons 29 to 30 : sense :
5' -cgagtgcgtccaggtgtact ; antisense : 5' -cttcccttgcgttccaggc
; exons 31 to 32 : sense : 5' -gaaggccaagcccaagtccc ; antisense :
5' -agccatgaccagcttcagca ; exons 32 to 33 : sense :
5' -tgctgaagctggcatggct ; antisense : 5' -cctgcagcacgcccgaagggt
35 ; exons 33 to 34 : sense : 5' -tccttcaagcgctccatgg ; antisense :
5' -tagtctggccacgcccgtac ; exons 34 to 35 : sense :
5' -ccggtcagtacggcgtggcc ; antisense : 5' -agatctccagtgcgcaggct

; exons 35 to 36 : sense : 5'-tgagctcggtccttccgg ; antisense : 5'-tccacgcaggagcagacccc ; exons 36 to 37 : sense : 5'-tcagacggcaccatggccag ; antisense : 5'-cttgcccattggctcggtt ; exons 37 to 38 : sense : 5'-ctctatggaaggctcgagtg ; antisense 5 : 5'-cggtgttgcaggatgtt ; exons 38 to 39 : sense : 5'-ctgacacccatccggctcttc ; antisense : 5'-ggcaactctctcggttgg ; exons 39 to 40 : sense : 5'-ggagatcaagctttgtatgt ; antisense : 5'-gtccttagcagcttcctcct. The following introns were determined by sequencing : exons 2 to 3 ; 3 to 4 ; 14 to 15 ; 10 15 to 16 ; 19 to 20 ; 20 to 21 ; 30 to 31. The following introns were determined by restriction mapping : exons 1 to 2 (using the following oligonucleotides as probes : exon 1 : 15 5'-cgccctgcggacatcgtcggcagc ; T3 : 5'-aattaaccctcactaaagg ; T7 : 5'-gtaatacgtactcactatagggc) ; 8 to 9 (using the following oligonucleotides as probes : exon 8 : 5'-gctttcaggttcttctgc ; exon 9 : 5'-aagaaaagagactccgaagt) ; 16 to 17 (using the following oligonucleotides as probes : exon 16 : 5'-tgagccacagatgctgacaaa ; exon 17 : 5'-gtactgtaagcacggtcacc). The results of the cloning, sequencing and mapping experiments 20 demonstrate that the 5.2 kilobase cDNA for the human DNA MeTase, is organised as 40 exons and 39 introns, with completely conserved splice acceptor and donor sites (Figure 5), on 60 kilobases of chromosome 19p13.2-13.3 (Fig. 4B). This gene can therefore be classified as a "large gene" 25 similar to Rb (70 kb) and apolipoprotein B (79.5 kb).

The functional domains of the DNA MeTase appear to be grouped together as a number of small exons and introns separated from neighbouring domains by large introns (Fig. 4B). First, exons 6-8 code for the nuclear localization signal and 30 exist within an isolated cluster that contains exons 2-8 and flanked by the large introns 1 and 8 (12 and 11 kilobases respectively). Second, the region described to be critical for targeting of the enzyme to replication foci (FTR) is coded for by exons 13-20. These exons are organized into two 35 distinct chromosomal regions, exons 13-16 make up the first region, and exons 17-20 make up the second, and are separated by the large intron 16 (6000 bases). Third, the region

responsible for zinc binding is coded for by exon 22, and in its genomic organization, along with exon 23, is isolated by the large flanking introns 21 and 23. Fourth, the catalytic domain of the enzyme is coded for by exons 30-39. The 5 catalytic domain of all of the known CpG methyltransferases share 10 conserved motifs of which 1,4,6,8,9, and 10 appear to be essential for catalytic activity. Conserved motif 1 is entirely contained within exon 31 and codes for the AdoMet 10 binding peptide. Conserved motif 4 is entirely contained within exon 32 and contains the Pro-Cys motif that catalyzes methyl transfer. Fifth, two postulated translation initiation codons exist (Fig. 4B) and the genomic organization of the exons in which they reside suggests that they form distinctly 15 different structural motifs. The antisense oligonucleotide of the invention hybridize to the target intron-exon boundary by Watson and Crick hybridization and effectively mask the splice junction. There is confidence that this approach can be successfully exploited for DNA MeTase because the gene offers 20 78 unique intron-exon junctions (Fig. 5) for antisense oligonucleotide development.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Szyf, Moshe
Bigey, Pasqual
Chandan, Sham R.

(ii) TITLE OF INVENTION: DNA METHYLTRANSFERASE GENOMIC
SEQUENCES AND ANTISENSE OLIGONUCLEOTIDES

(iii) NUMBER OF SEQUENCES: 70

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: HALE AND DORR LLP
(B) STREET: 60 State Street
(C) CITY: Boston
(D) STATE: MA
(E) COUNTRY: United States of America
(F) ZIP: 02109

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: PCT/
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Keown, Wayne A.
(B) REGISTRATION NUMBER: 33,923
(C) REFERENCE/DOCKET NUMBER: 106.101.187PCT

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (617) 526-6000
(B) TELEFAX: (617) 526-5000

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

~~TCGGGGCAGGGTGGCGGGTAGGAGGCAGGCCGAGCGGCTGGCTGGAAGAGAGTGT~~
~~GGTGTGTCGGACGGCAGCTCCTGTGTGCTCCAAGGGATGAGCCTCGTCGGCGT~~

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

TTCCCCATGTTTCTTAGGAGCACTATAGTTTCAGGTCTATGTTAATCTTTAATAAGTTTGTTTT
TGTATATGGTGTAAAGGTCAAGGGTCAACTTCATTCTTGTATGTGGTATACAGTTCTCAGCACCATT
TGTTAAAGACACAACTTTCCCCATGTTCTGGTGTAAAAAAAAATCTGGCTGGTACGG
TGGCTTAGGCCTATAATCCCAGCACTTGGGAGGCTGAGGCAAGTGGACTGCTTGAGGCTAGGAGTCCC
AGACTAGCCTGGCCAACATGGTAAACCTGTCTACCACCGAAGATACAAAATTAGCCAGGCGTG
GTGGAGTACGCCGTAAATCCCAGCCTAATAGGAGGCTGAGGCATGAGAATCGCTGAACCTGGGAGG
CAGAGGTGAGCAGTGGCAAGATCTCACCACGTGACGCCAGCCGGGTGACAGAGTGAGGCAGGGTCT
TACCCCTGCGCCAGGCAGGAGTCCAGTGGCCAATCATGGCTCATGCCAGGTT
CAAGCCATCCTCCCACCTCAGCCTCCAAAGTAGCTAGGATTACAGGTGTGTGACCATCCCAGCAA
TCTTGTATTTTGTAGAGATGGGTATCCCTATGTTGCTCAGGCTGGTCTTGAACCTCAACCTCAAGCGA
TCCTCCCACCTGGGCTCTCAAAGCACTGGGTACAGGCGTGAGCCACTGCGCTGACATGGTGTCTT
AATTATCTTACTTTTATTTTGTAGACAAGGTCTGCTCTGCTCCAGGCTGGAATGTAG
TGGTACAATCATGGCTCACTGCAACCTCTGCCCTCCGGTCAAGTGATCTCCTGCCAACCTCTGG
AGTAGTTGGACTATGGCACATGCCACAACGACTAGCTAATTGTTTCTTTCTTCTTCTTCTT
TCTT
CTCAAGCGATCCTCCCACCCCTGGCCTCCAAAGTGTGGATGACAGGCGTGAGCCACGTGGTCTTA
AAAAAGGCAACAAAAACCCCCACACACTGGGTATAGAAGTGGCATGGGCTCTATACACTGTGAG
ATTCTGGTACTAGCTACAAATTCTGTATACTCAAGATTTCTAGAGTAGGTGGCAATTACCCGTT
TACAGATGAGGACACAGAGGCTGAGCGTAGTGACCCACCTAAGGTGCGTATAGCCAGCAAATAGATGG
AGGTGGATTGGAAACTGAGGACTTACTCAAGGCTCTCAACCCCTGGGGGCTTCTCGCTGCTT
ATCCCCATCACACCTGAAAGAATGAATGAATGAAATGCCCTGGGACCGTCCCTGCCAGGAACG
TGGAGCTGGACGCCACTCGTCCCGTGGGGGGGTGTGCCCCGCTTGCATGCGT
GTTCCCTGGCATGGCCGGCTCCGTTCCATCCTCTGCACAGGGTATGCCCTCTCCGT
TTGGTACATCCCCCTCCTCCCCACGCCCGACTGGGTGGTAGACGCCCTCCGCTCATC
GCCCTCCCCATCGTTCCGCGAAAAGCCGGGCGCTCGCTGCCGCCCGCGT
CTGCTGAAGCCTCCGAGATGCCGGCGTACCGCCCCAGCCGGTGCCACACTGGCC
GTCCCGGCCATCTCGCTGCCGACGATGTCCGAGGGCGTAGGTACCATGGGGGGAACACG
GACTCAGGGGGACAGGCAGGGCGCTGGGTGGGGGTGCTCCCCCTGGGGTGGCGTGGCGTGGCT
GACAGACGGGGCGCATGGCTGGGTGGTGCAGCGCAGTTGGCGCGGCAGGGTGGCACTT
CCGGTCGCGCGTGCCGGCTGTTGGCGCCAAATGGACCGTGGATTCCCCCGTACGCCCTGGTGG
CTAGAAACTAGGCAGGGTGGCCTCTTTGATCCCCAAATACAGC

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AGGAGGTCTTGCCTC
AAACTTGCCGGCTAAAGGACATACATTATTACCTTATGTCCAGGGTCAGAAATCTGATGC GGGTTTCAC

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

TCTAGAGCTGGGGCGGACGTCAATTAAACCTCAC~~TAAGGAGTC~~ATTC~~TC~~
ATCGCCCTATGTTGTCAGGGCTGGACTCGAACCTCTGCCACAAGGCATCCTCCACCACAGCCTCC
TQAGTAGCTGGGTTACAGGCACGCAGCACGGGGACTGCACCGCTTTGTTCTTTTATTTTCCC
TCTTGTCCCTGAAAGAGTCAGCTACTAATTGTCAGTAATCAAATCAGACCACGATTCCCAGGAAA
CTCCTGGCAGTTCTACATTAGGAATGACTAGCTAGAGACATCCTGAAGAATGAGTTATCCGGGAGGC
GCCACGACCTCCTCTAACCTCACCTCTATCTGCCCTCTGTGGGTACCCCTGCTCCCTGGATGCTTG
ACTCCCCCATTCATCCTCAAAATGCCACCACCCCCCACCAGGCCCTTAGGAACATCAGCTGGCTGTT
CCCACAGTGTCTGTGGCCCTGGCTACTCATCTGACACTGGCCACTGTGGCACACCTGTTATGG
GCTGTTGTCAGACCCAACCTGGAGAAAGACCAGCTGAGGTCAATTCCCTAACGGAGTGCCCCAACTAT
ATGACCTGCCCTCTTCTGGTATCTTTGAGTCAGGGCTCACTCTGTCCTAGATTGGAGTGCA
GTGATGCAATCAGGCTCACTGTGGCCCTGACCTCCCAGGCTCAGGTGATCTCTCAGCCTCCAA
GTAACGGGACCAAGCACATGCCACAAACCCAGTTATTTTATTTTATTTTATTTTATTTGAA
GACAGAGTTCACTCTGTTGCCAGGCTAGAGTGCAATGGTGTGACAGCTCACTGCAACCTCTGCC
CCCGGGTCAAGTGATTCTCTGCTCAGCCTCCAAGTTGCTGGATTACAGCCACCCACCACCCACGC
CTGGCTAATTTGTTATTTAGTAGAGATGGGTTCGCCATGTTGCCAGGCTGGTCTCAAACCTTG
ACCTCAGGTAATCCACCCACCTGGCCCTCAGGTAAATCCACCCAACTGCTGCTGTATGTTGGATTCCA
GGCATCAGCCACCAAGCCCAGCCACTAATTGTTATTTGTTAGAGATGGAGTTGCCATGTTCCCA
GGCTGGTCTGAAGCCTGGCTCAAGTGATCCGCTGCCCTGGCTCCAAAGAGCTGGGATTATAAGC
GTGAGCCACCATGCCCTGGTCTGGTACCTTAAATATAAGGCTGGCATGATGGCTCATGCCGT
AATCCCAGCACTTGGGAGGCTAGGCAGGTGGATGCCCTGAGGTGGAGTTGAAACCTAGCCTGA
CCAACACGGAGAAACCTGCTCTGCTAAAATAAAAATTAGCTGGGTGATGGTGGTGCATGCCGT
ATCCAGCTACTCGGAGGCTAGGCCAGGAGAATCGCTTGAACCTGGGAGTCGGAGTTTGGAGCTGAGA
TCACACCATTGCACTCCAGCCTGGCAACAAGAGCAAAACCTATCTCAAAAAAAAAATATATA
TATATATATATATATACAGCTATATAGCGTATATATATACACACACATATGTATACATAT
ACGTATGTATACACATATACGTATATACACATATATGTATAATACACACATACGTGTAT
ATATACTGTTATATATATGCACTGCCAGACAAGGTGACTCATGCCGTAACTCTAGCACTCAGGAGA
CTGAGGCAGGCCATTCACTTGAGGTCAAGAATCTAAGACCAGGCTTAACCAACATGGTAAACCC
TCTCTACTCAAAATAACAAAAATTAAACGAGGCTGGCACCTATAATCCCAGCTACTTGGGAGGGCTG

AGGTGAGAGAATCACTTGAACCCAGAAGGTGAGGGTTCAGTGAGCTGAGA TCGCACCACACTGCACTCC
ACCTGGGCAACAGAGCGAGACTCCATGTCTGCTG TCTGTCTATCTATCTGTATAATGTATATGTATGA
TGTATATATGTGTGTATATATA TACACATATATACACATATACACACATACTCTGTTACAGAGC
TGCTGTGTGTGTGTATATATACACATATGTATATACACATATACACATATATGTATATATA
TACACACATATATACACATATA TATGTATATATACACATATACACATATACACATATATGTATATATA
ATACACATATATGTATATATACACACACACACATAATTGTGTACAGAGCTGCTATG
TAATCTCACAATCATCAGAAAAATGACCCCCAAAAGGGGAACCTGTTAGATCAGATGACTCTTAGC
ATTAGGCATTCCAGTAGGACACTCTAGACTCTGCGGGGAGACAAAAGCCAGCTTAGTTCTAACA
CTCATATGTAAACTGTTGTCCAAACTCTTGAAGACTGTGATATTCTACAGGAAATGAAGTT
GCTTAACAAGTGTGTATTTCTCCCTATTCTCCTCCAGG₇₈CTCAAAGATTGGAAAGAGACA
GCTTAACAGAAAAG₁₁₄GTAATCTCCCTTAAATTTCTTACCAAAACTGACTGACACACTT
TGTGGCTCATAAAAAGAAATTGTTCTTAAATGGATTGCACTTTCCATGGAGTTCAAAGATA
ATTGGATATCTGTTAAATGTCAGCACTAATTGCTGCTAA TAGTTGGTGGTGG TGGTGTGTTTTT
GTTGTTGTTTGTGTTTGAGACAGAGTCTCACTCTGTCACCCAGGCTAGAGTGAATGGCATGATCTC
GGCCTCACTGTGACCTCTGCCCTCCGGATTCAAGCTGTTCTGCCTCAGCCTCCCAAGTAGCTGGGA
CTACAGGCACGCACCACCATGCCAGCTAATTCTATTAGTAGAGATGGGTTACCATGTTGG
CCAGACTGGTCTGAACGCCCTGCTCGTGATCTGCCACCTGGCCTCCAAAGTGTGGAATTACAGGC
GTGACGACCATGCCCTGGCCAGGTTTTTTTTAACCAACTCTCAGTTCTAAACAACACTCTACTCTG
GATTGTAACCTGTCCTGGTAACACTGTTTATTGTGTTTTGTTATTGTTGAGATAGGGCTCTCATTCT
TAGGCCAGGCTGGAGTGCAGTGGCACAATTGGCTACTGCAACCTCGCCTCCAGGCTCAAGTGA
TTTCCACTCAGCCTCTGAGTAGCTCAACTACAGGCTCAAGGCCACCATGCCAGCTAATTCTAA
TATTGTTGTAAGATGGATTGTCATGTTGCCCCAGGCTGGTCTGAACCTGGGCTCAAAGCAAT
CCACTTGCTCGGCCTCCAAAGTGTGGATTAGGTGTGAGCCACTGTGCCTGGGGGACACTTTA
CAGAAGCACAGTATTCTTATAAAACCATGATATGTCTCCATCTCACCTCAGCTTCCATTCTC
CACTTGAGACAGGAGTGAAGTGAATCTCTGACGAATTCTGCAAACACATTGACTGTTAGTGT
TTGACTGAGACAGCATTGCCATTCACTCATTGTGATGTGATCAGGCAGCTCAATAATTGTGATT
AGTCCACTAGTGAATAGCTGGAAATGTGGTACTGCTAAACCTATATCCTCCCTAGG₁₁₅AATGTG
TGAAGGAGAAATTGAATCTCTGACGAATTCTGCAAACAGAAATAAGAATCAGTTAT
GTGACTTGAAACCAAATTACGTAAAGAAGAATTATCCGAG₂₂₂GTAAAGTCAGITCTCAGCAT
CCTAGCCTCTAGAAAAATGTCTCCTCTAGTAACCTGCTGTGACCAGGGAGGCAGCAAGATCCCCAGC
TGTCTCATTGCCCTGATGATGATGATGATGATGATGATGAGAAGAACACATGTGTTCTGCTCTGACAC

Augo 39

GTGTTACATTCACTGCTACTAATTATCCTGTCCGTCTAGG₂₂₃AGGGCTACCTGGCTAAAGTCA
AATCCCTGTTAATAAAGATTTGTCCCTGAGAACGGTGCTCATGCTTACAACCGGAAGTG
AATGGACGTCTAGAAAACGGGAACCAAGCAAGAAGTGAAGCCCCTAGAGTGGGAATGGC
AGATGCCAACAGCCCCCCCACCCCTTCAAACCTCGCACGCCAGGAGGAGCAAGT
CCGATGGAGAGGGCTAAGC₄₄₂^{8160 63}GTAAGAGCAGATGATTCCCTTTATTTAATTGTTTGAGATGGAG
TCTCACTGTGTCAGTCTGGAGCACAGTGGTGTAACTCGGCTACTGTAACCTCTGCCTCCAGGT
TCAAGAGACCCTCCTGCCTCAGCCTCCAAAGTAACT

(2) INFORMATION FOR SEQ ID NO:5:**(i) SEQUENCE CHARACTERISTICS:**

- (A) LENGTH base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:**(iii) HYPOTHETICAL: NO****(iv) ANTI-SENSE: NO****(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:**

*5'GCCAACATTAGCAAGCTG
GTGTTGACTAGAAATAAAATGCAAAGATGCTAGTCCTAGAACCTGGCTTCCTGCAATAGCTTAGTA
ATGTTGAACIGCATTATTGCTGTGGCTTCTATTGATAGTGGCTTTTTTTCTTTTAATGCTTTTCT
TCTTAAACAGC₄₄₃^{OLIGO 64}TGAACCTTCACCTAGCCCCAGGATTACAAGGAAAAGCACCAGGCAA
ACCACCATCACATCTCATTGCAAAGGG₅₁₈GTCAGTATACTGATAAAATTGGCGGCTGCCTTTT
AGGGGCCGGCTGTTGGATGGAATTGGTAGGGCGTCACGTGGCAATTCTGTCTCCGTGTGTATA'*

(2) INFORMATION FOR SEQ ID NO:6:**(i) SEQUENCE CHARACTERISTICS:**

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:**(iii) HYPOTHETICAL: NO****(iv) ANTI-SENSE: NO**

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TCTCTGA~~C~~ACTAGCAGCTGTTGATCGGTGTTAGACCCGTGATTCTTAGGACTTACA
 AGATGGCAAGACAAACATTCTAAACCCGTATTAGAGAAACATTAAACTTGAAAGCCTTTCAACATCC
 TGGTGAATGAGGGTCCACTTCAGGCCAGCTGGAGGCCTAGGGCTTGTCCACTAATGGTGGCCTCAC
 TGTGTGACAGC₅₁₉^{OLIGO 65}CTGCCAACGGAAACCTCAGGAAGAGTCTGAAAGAGCCAATCG
 GATGAGTCCATCAAGGAAGAAGACAAAGACCA₅₉₇^{OLIGO 66}GTAGGGCCAGTGCCTTCATTCTGACT
 CTACCTACTGGTGTATTGATGATTGTGACTTCATATGTGTTCTGTCAGTAAATAAAAACCCGTGTC
 TAGGGCTCTATTAGGGCTCTCCAGAGAGACAGGACCAATAGAATGTATATGTGTATCAACGTATAG

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: both

(ii) MOLECULE TYPE:

- (v) FRAGMENT TYPE: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GTTTGGGTTGGTGGGATTAATACCAAGTAAGAGTTCTCAGATCTTCTCCCC
 TTTCCCAGGCCCTTCTTCCACTCTGCTCTAACCATGTCAAATGTGTTAATATTCAACTCACAC
 TTTGGTGTGACCTCCCTGAAACCAAGTATTCTAATCTTTGTTCTCCCTCCACACAGG₅₉₈
 ATGAGAAGAGACGTAGAGTTACATCCAGAGAACG₆₃₂GTAAGAATAGTTACTACCTTCTTT
 TGTTCTACGAGTTGTGAATCTGATCACAAACTTTCAAGAAAGTT

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

CAGGGCTCCG
AGATAAGAAGATTGCTTTGGGAAAAAGGGAGCTTATGAAAAGCTGTTCTTGGGAAGCTCCTGG
CACTCACACTGGGTCTGTGTATTTGCTTGACAGA₆₃₃^{D160 C7}GTTGCTAGACCGCTTCCTGCAGAAG
AACCTGAAAGAGCAAAATCAGGAACGCGCACTGAAAAGGAAGAAGAAAGAGATGAAAAAA
717GTAAAGCTATCACCTCTAAG

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:
TACAGGCCTGAGCTACTGTGCCCACTGGTAGACAGTCTTTA
CTCCCACCACTGACTCTAGAACATCAGTCAGGTGTTTATTCATAGGACACTTAAAGAAAGATCCA
AACCAAATGGAAAAAATTAACTTGTCTTTTCCCTGCAACTTAGG₇₁₈AAGAAAAGAGACTCCGA
AGTCAAACCAAAAGAACC₇₅₂GTAAGTGCAGCGAACCTGCCTTGTGCTTGTGAAACTGAATTG
CTAACATAAGTATCTGGTAAATAACGGGTTGGTGTGGAACAGTGGCGCTAATCATATGTCTTTATG
TGGGCAAGTTCTGCTTGTGAAAGGTGAGACCACCTGAAGTGAAGGCTGAAGTTAACCTTTAACTTTA
ATTTAATTAAATTAAATT

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CTTCAGTTCTGTTGGGTGTTGGTCTTGGTTGACTTCGG

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TGAGTCCTGAGTAGTAAATCGTCTGGCTTCTGCAGTGAAGACAGGAGAGGCAG
 CCTGTCCTCTAACCTGGGGAGGAGCTTGTGTCAGCCCTTAGGAGCTTGGCCCCGGTGCAGGGCCCC
 CCCCCAGCTGACCAGCCTGTGTGTGTTCTGTGACAGA₇₅₃^{750 69}ACACCCAAACAGAAACTGA
 AGGAGGAGCCGGACAGAGAACGCCAGGGCAGGCGTGCAGGCTGACGAGGACGAAGATGG
 AGACGAGAAA

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AGAAACTAATTTTCCCTCTTATCTCTACCTC
 CCCCTTATTTCTGTCA₈₄₁GGATGAGAAGAACAGAACAGTCAACCCAAAGATCT₈₇₅CAA
 GTGTTAAAATGCTTGTGCTTTGTGTCATCTGGATCACTAGAAAGCCTGTTAGGCAAGGTGTGGTG
 GCTTGCACCTGTAATCCAGCTAAAGGGAGGCTGAGGTGGGTGAATCACCTGAGGTCAAGGAGTCGA
 GACCAGCCTAGCCTGGCCAACATGGTGGAACCTGTCTGTACTAAAAA

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

(GACTATAAGATTGTATTCTATGACTTAGATGGTAGAGTGAGTCAGAGCTCACCTGCTGGCCC
 TCTCACTGCCTCCCTCCCTCTCTGTGGATGATAATCACTTATAACAAAGTCTTAAACACCGAAGCA
 CTATCTGGGAGGAAAACACTCTTAGCCTTAATCCTTTGTTTCCCTGTGTAGG₉₅₈AGAAGAG
 ACGCAAAACGACCCCCAAAGAAC₉₉₂GTAAGAATTATTCTTGACATTATCCAAGCAGATGTT
 AATGTTAAAATGATGGTTCTAGAACAAAA

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CAACGATCTGTGATTTTTTCCC
 CCAGA₉₉₃ACGGAGAAAAAAATGGCTCGGCCAAAACAGTCATGAACCTCAAGGTAAACAT
 CTGCCCCGAATAAGCCGGTGGCGGGCTCACGAGCGGCTGGAGCTGCTCTGAGTGCCATCATCT
 GTGTTCTGCTCCCACAGA₁₀₃₉⁰⁰⁶⁰⁴⁰CCCACCCCTCCCAAGTGCATTCACTGCGGGCAGTACCTGGA
 CGACCCCTGACCTCAAATATGGGAGCACCACCAAGACGCG₁₁₁₉GTTCGTACAGCTCTTCC
 CAGCCCTCCTCTGCTGTCCCTGTCCACTGCTCACCAAGCCCCGTGTCCCTCAGG₁₁₂₀TGGATGAG
 CCACAGATGCTGACAAATGAGAAGCTGTCCATTTGATGCCAACGAGTCTGGCTTGAG
 AGTTATGAGGCGCTTCCCCAGCACAAACTGACCTGCTTCAG₁₂₂₉GTAAGTGCACTTCTGTG
 GCATGTTGCTCGTGGAGGAGGCACATCCCCAGAGG

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CCATCCTAATACGACTCACTATAG
 GGCTCGAGCGGCCGCCGGAGGTCTCTCTGTCTTCACTAAAGAACGTGCTCCGAATGTC
 AAGGGGCATCTGGACAGTGGCCGCAGTGTGAGATTATGCCAAAAGGAGGCAGAAGT

 CTTCCCTCCCACATCCCTTTCACACTGTTCTATAACCTGCTTATTTCTAAATTGAGG
 TCTAACTCGTATAATATAAAATTAACCATATGAGGTATCTTGAATAGGTGAATTCAAGGT
 ATAGAAAGCAGATTGGTGGTGCCTGGGGCTGAGGGCCGGTGGGAGGGAGACT
 GGAGAGTGACTGCTACTTGATGGGAATGAGGCTTATTAACATTGAGTGACAGAAATGT
 TCTGCAGCTGAATAGAGCTAGTGGCTGCACTGCATAGTAGAAGGTGTTCTAGAAACCGGT
 ATTTCCCGCACTGTAAGTCTGACTGATCTTGGTGTGCTGTCAGACACACATAACT
 TGATGCTTAGGTGGAGAATAAGGTAGAAACTCTGGGTGATAGAACGCTGTCTTAATCCA
 GTGTTCCCGCAACCAAAATGAGTGTGGGCCAGGCATGGTGGTCAGCCTGTAATCC
 CAGCACTTGGGAGGCTGAGGTGGTAGATCACTGGAGATAAAGAGTTGAGACCAGCCT
 GCTACACATAGTGAACACCCGTCCCTACTAAAAATACAACAATTAGCCGGCATGGTGGT
 TCAGGCCGTAAATCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATTACTTGAACCCGGG
 AGGTGGAGGCTGCAGTGAGCCAAGATTATGCCATCGCGCTCCAGCCTGAGGGATAGAGC
 AAGACTCTGTCTCAAAAACAAACAAAAAAGAGTGTCAAGACTTGTACATTCTCTCATTT
 CTCGTGCCTGATATGAAGTCTGCACGAAGACCCCTCACGGCTTAGCTGGTAAGCATGTG
 CTTTGT~~TT~~¹²³⁰_{OLIGO 41}CTGTCTAGT₁₃₄₈GTGTACTGTAAGCACGGTCACCTGTGCTCCATCGACACCC
 GGCCTCATCGAGAAGAATATCGAACTCTCTTTCTGGTCAGAAAACCAATCTATGAT
 GATGACCCGTCTTGAAG₁₃₄₈GTAAGGAATAGTCCGGGATTATGTTGGGCACACTTAAAAAC
 AGCCAGGCAGGTTGGCTCACATCTGAATCCTAGCACTTGGGGCTGAGGCCAGAGGATCACTTGAGC
 CCGGGAGTT

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: .

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TTTAGTCCATTCCTTTCTGCTCTAGG₁₃₄₉TGGTGTAAATGGCA
AAAATCTTGGCCCCATAAATGAATGGTGGATCACTGGCTTGATGGAGGTGAAAAGGCC
TCATCGGCTTCAGCACCT₁₄₄₁^{0160 43}GTAAGTGTGGCCCATCATAGGCTGGCCGGGGTCTGAAAGGGG
CCTTCATGTTCTCCTTCTGGGGGCTGACGGGGCTCTGGTGGAAATTCTCAGCAGGCTTGCAGAAGGCC
ATGTGACTGGAACCTAGCAGGTTCAAGTTGGGGTAGATCTTTGTGTAGTTAGTAGG

(2) INFORMATION FOR SEQ ID NO:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CGCTCTCTGGCTGGCTCAGACAGGCTCTCAGAACAAAGCCAGCTATGATGTGTTGCCCTATGTTCTGACATTTGGTACGGGATGACTTTAGACTGTGGTGA
GTTGGTAGACTCCTCCATGCCCTGTGGCCACTGTAGGCGCCATCAGATTCCAGCCCCTTCCACACCTCCCTGTCGCCCCAGC₁₄₄₂ATTTGCC
GAATACATTCTGATGGATCCCAGTCCCAGTATGCGCCCATATTGGGCTGATGCAGGAG
AAGATCTACATCAGCAAGATTGTGGTGGAGTTCCCTGCAGAGCAATTCCGACTCGACCTAT
GAGGACCTGATCAACAAGATCGAG₁₅₉₃GTAAGAGATCGAGGGCCTCAGCATCCGGATTCCA
CTGGAAACTTGCCCTCAGAACCAACAGCAGACACTGTTCTCAGTTGGATTAGGCCAGTTGGCTTAAGCA
TGAGAGAAACCTGTTCTTCAAGA₁₅₉₄CCACGGTTCCCTCTGGCCTCAACTGAACCG

CTTCACAGAGGACTCCCTCCTGCACACGCGCAGTTGTGGAGCAGGTGGAGAGTTA
TGACGAGGCCGGGACAGTGTGAGCAGCCATCTTCCCTGACGCCCTGCATGCCGGACC
TGATCAAGCTGGCTGGGTACGCTGGACAGAG₁₇₈₁GTAAGGATCGGGCTGGGACCAAGAGTG
AAGACTGGAGACCGGGGAGGGTAGAGCATGCCACATCCCTCTGTCAGTCCTGAGATGCTGAA
CCTCTCCGTAGG₁₇₈₂CGAGCCCAGCGAGGCAGACCATCAGGCATTCTACCAAGGAA
GAAGGACAGGGGACCCACGAAAGCCACCAAGCTGGTCTACCAGATCTCGATA
CTTCTTCGAGAGCAAATTGAAAAGGATGACAGAGAAGACAAGGAGAACGCCCTTAAG
CGCCGGCGATGTGGCTCTGTGAG₁₉₆₈GTAACCTCACCTGTGGGTGCTCCGCTCCCTAAGGTG
GCCCAAGCCTCTGGCCTGATCTGAGGACTGCTCCATCTTCTCTGTGGCTGAGACTCTGGCTGCTAAA
TGTGACCCCTGAGACAGAAATTGTTGTGG

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: .

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CTGTGCCAGCCTGTTGCCTTTATGCCTTTTAG
G₁₉₆₉TGTGTCAGCAGCCTGAGTGTGGAAATGTAAAGCCTGCAAGGACATGGTAAATT
GGTGGCAGTGGACGGAGCAAGCAGGCTTCCAAGAAGCGGAG₂₀₆₆GTAGGTCA_{OLIGO 46}GGCCAGTC₂₀₆₆
TTCCTCTGTGGCAGAGGACTTGCCAGCTGGCAGATGCACTGTGGAGAAGGGCCGTATGTGAGG
ACAGCACCAAGGATTCCCTCG

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: :

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AGACCTGTCCTGTTATGAAGAAAACA GCCCCGGTTG
GTCTTACTTAGAAAAGGGGCCTAGGTATAACCAGTGACATTGCAGG

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

G₂₀₆₇TGTCCCCAATATGGCCA
TGAAGGAGGCAGATGACGATGAGGAAGTCGATGATAACATCCCAGAGATGCCGTACCC
AAAAAAATGCACCCAGGGGAAGAAGAAGAACAGAACAGAACATCGCATCTCTGGGTGG

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 394 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

AGAAGCCGTCAAG₂₂₁₄ **GTAACCCTTGGAGTCCCCTGGTTCA**_{OLIGO 47} **GTCCTCACTGCA**
AUTCAAGGCCAGCAAAGACCCTCAGAATGATCCTCCATGA_{ACTTATGCTCTCATTTTCA}**G**

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: :

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

A₂₂₁₅**CTGA**
TGGGAAGAAGAGTTACTATAAGAAGGTGTGCATTGATGCGGAAACCCCTGGAAGTGGGGGA
CTGTGTCTCTGTTATTCCAGATGATTCCCTCAAACCGCTGTAT**CTAGCAAG**₂₃₃₀**GTTTGCAT**
SEQ ID NO 23 OLIGO 48

(2) INFORMATION FOR SEQ ID NO:24:**(i) SEQUENCE CHARACTERISTICS:**

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:**(iii) HYPOTHETICAL:** NO**(iv) ANTI-SENSE:** NO**(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:**

CTC

CCCATGCCGTCTCTATTCCAGG₂₃₃₁GTCACGGCGCTGTGGGAGGAAGACAGCAGAACGGCA
GATGTTCACGCCACTGGTTCTGCGCTGGGACAGACACAGTCCTGGGGCACGTCGGA
CCCTCTGGAGCTGTTCTGGTGGATGAATGTGAGGACATGCAGCTTCATATATCCACAG
CAAAGTGAAGTCATCTACAAAGCCCCCTCCGAAAATGGGCCATGGAG₂₅₃₅GTGAGTGC
CTGGTGTCCCTCGTGAGCCC

(2) INFORMATION FOR SEQ ID NO:25:**(i) SEQUENCE CHARACTERISTICS:**

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:**(iii) HYPOTHETICAL:** NO**(iv) ANTI-SENSE:** NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GACCUAACCGACGATATCTTGAGTCTCCCAAGG₂₅₃₆GA
GGCATGGATCCCGAGTCCCTGCTGGAGGGGGACGACGGGAAGACCTACTTCTACCAAGCT
 GTGGTATGATCAAGACTACGCGAGATTGAGTCCCTCCAAAAACCCAGCCAACAGAGG
 ACAACAAGTTCAA₂₆₆₉GTGAGCACTGGGCTGGACTCGGGGTCA₂₆₇₀GCAGGCAC₂₆₇₁TTCA₂₆₇₂AGCCCACATC
 ACTCCCTTTCCCGTGTGCTTCCG;
SEQ ID NO 25 0160 50 ←

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AAGCTGGCAGTAGCTGCTGCGGCCACTGCCGGCC

ACCTCAGGGCCTTA₂₆₇₀TGTTCTGTCCTTGTTCCTTCAGA₂₆₇₀TTCTGTGTGAGCTGTGCCCGTC
TGGCTGAGATGAGGAAAAAGAAATCCCCAGGGCTGGAGCAGCTCGAGGACCTGGAT
 AGCCGGGTCTCTACTACTCAGCCACCAAGAACGGCATCCTGTACCGAGTTGGTGTGATGGT
 GTGTACCTGCCCTGAGGCCTTCACGTTCAA₂₈₄₃GTAA₂₆₄₄GTGCCCCCTCGGAGCAGCCGGGGC
 CAGGGG

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 489 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AAATCATTCTTAGGGTACACACCTACCTTAATTATCAGGTGCTTGACTTT
AAATGGTTATTTCACTGGTCAGTCATGCCTGACTGACCACTGCAAAGGTGGAAGGTTCAATTGATGTCAA
GTGGGTGCTTCTCTGCAGC₂₈₄₄^{0160 5a}ATCAAGCTGTCCAGTCCCGTGAAACGCCACGGAAGGAGC
CCGTGGATGAGGACCTGTACCCAGAGCACTACCGGAAATACTCCGACTACATCAAAGGC
AGCAACCTGGATGCCCTGAGCCCTACCGAATTGCCGGATCAAAGAGATTTCTGTCCC
AAGAAGAGCAACGGCAGGCCAATGAGACTGACATCAAATCCGGGTCAACAAGTTCTA
CAG₃₀₆₅GTCAGCAGAGGCCCTGTTCTCGAGGCCACAGACTCTTAGAAGGCTCTGCTGAAAC
AAGGTTGTGG.

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

AAAAGGAGAGCTCTAACGAGGCCTACTCCGCTCGCAGG₃₀₆₆CCT
 GAGAACACCCACAAGTCCACTCCAGCGAGCTACCACGCAGACATCAACCTGCTACTG
 GAGCGACGAGGAGGCCGTGGACTTCAGGCTGTGCAGGGCCGCTGCACCGTGGAGT
 ATGGGGAGGACCTGCCGAGTGCCTCAGGTGTACTCCATGGGCGGCCAACCGCTTC
 TACTTCCTCGAG₃₂₅₈GTGGTGCCCTGCTTGCTAGAGGAAGGCTCGGGTCAAAGTTGCCAGA
^{OLIGO 53}
 AGGAGTCTGATGTCGGTTATACACAAGCGGCTGGCTGCAGGGTTAGCTTTGTAAGAAGTGGGT
 GGTTGGCTGACGTGAAGCTGTTCTGCAGGAGCTTACGGGGG

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: c.

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GTCAACTACTCTATTG
 GTGGCTAATTGGTCATGGCCCCACTGAGGAGAATTAAGTGACTATCAATTGCCCTCTTACTAGTCTGGCTT
 TAGAGAGGGACAGTGGCGTTCTCTCCAAACGATTGCAGTTCTCTCCTTCAAGG₃₂₅₉CCTATAAT
 GCAAAGAGCAAAGCTTGAAGATCCTCCCAACCATGCCGTAGCCCTGGAAACAAAGG
 GAAGGGCAAGGAAAAG₃₃₄₃GTACGTATTGTATGAGTTCTTCAAGTTATTCTCTGTAACCTG
 GAGGCTGCCGTGAATCCCTCAGTGTAAAACCACCTCTGGTGTACTGACTCTGGACAGCGAGGCCGC
 CTGAGTTAACAGCGCTTGAGAGCAAGGTGGACTTGGACTCTGAGGATCGGGTTAGCCTCTGGCCTC
 TCTCCCCCAGG₃₃₄₄GAAGGGCAAGCCAAAGTCCCAAGCCTGTGAGCCGAGCGAGCCAGAG
^{OLIGO 54}
 ATAGAGATCAAGCTGCCAAGCTGCCGACCTGGATGTGTTCTGGCTGCCGGGGTTG
 TCGGAGGGATTCCACCAAGCAG₃₄₇₂GTGAGCGCCCGTAGGCTCCATCTCTGAATACCTGGTAGC
^{OLIGO 55}
 CCAGACCGGGCAGGTGCTACCTGAAACGACTTCCAACCCGGTCACCTCTGATCTAAGAATCTTCA
 GGCCAGGCACG

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

ACTGCACGCCAGCCTGGGTGACAGAGCGAGACTCCATCTCAAAAAA
AAAAAAAAAAATCTTCTGGAGAGTTGAAAGCATGGCTTCGTTGATCTGCCAGG₃₄₇₃CATCTCTG
ACACGCTGTGGGCCATCGAGATGTGGGACCCCTGCGGCCAGGCAGTCCGGCTGAACAAAC
CCCGGCTCCACAGTGTACAGAGGACTGCAACATCCTGCTGAAGCTGTCATGGCTGGG
GAGACCACCAACTCCCGGGCCAGCGGCTGCCAGGGCTTCAGCGGCATGAACCGCTTCATTGCGCACCTACT
CGGCGGGCCGCCCTGCCAGGGCTTCAGCGGCATGAACCGCTTCATTGCGCACCTACT
CCAAGTTCAAAAATCTCTGGTGGTTCCCTCAG₃₇₅₅GTAAACGGTAGAAGCCCCCAG
TGGGCCAGACGGCCGGGCTGCGCATGTCAGCAGTGTCAATT

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31: GAAGCTCACAG

CTCAGCTCTCACCAAGGGAGAGACTTGATAACATTGTGAGGGGCTCCGGCACAGTGGCGTTCTTC
 CCTCTGTCTGTGGAGGTGACTCTGCAGTCTCTCCTGCCCTACAGCAGC₃₇₅₆TACTGCGACTAC
 TACCGGCCCCGGTTCTCCTCCTGGAGAATGTCAGGAACTTGTCTCCTCAAGCGCTCC
 ATGGTCTGAAGCTCACCCCTCCGCTGCCGTGGTCCGCATGGCTATCAGTGCACCTCGGC
 GTGCTGCAG₃₈₉₇GTGGGCCCTGGGCTGGGCGGGCAGACAGATGAGGCCAGCAGTGACCCGGCC
 AGCAGCCAGCCATCCCTACTGAAGGCAGGGTCAATGCCATAGGCCTGCCATCCAGGCAGCAGAGGC
 TGGCATGGTGTCTGTCCACTGGCGGATGAGGGAGATCG

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CGACTCAGCTGCTGAC
CCTGGGCCCTGGTCTGCCAGTCCAGTTGGAGTGTCCCCTGACGGTGGGTTGTCCGTCTCTCCC
CCACAGG₃₈₉₈CCGGTCAGTACGGCGTGGCCCAGACTAGGAGGCGGGCCATCATCCTGGCC
0160 56
GCGGCCCTGGAGAGAAGCTCCCTGTTCGGAGCCACTGCACGTGTTGCTCCCCGG
GCCTGCCAGCTGACGTGGTGGATGACAAGAAGTTGTGAGCAACATAACCAG₄₀₆₄GTAAG
TGGCCCCGTCGCTCCACACACTGCCAGCAGGCTCAGTAGCTCATGGGG

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

iCATAGC

CCCATCCCCCTTCCAGATGGATCCAGCACACTGCCACCCATGTGACCTCGGGAGTGCTGTGATCT
 CGGGAGAAGGCCATCTGAGCAGGCAGGGGGTGGCACCTGTGATGAGGGACAGCTGCTGCGTGCATCT
 CCAGAGGTGTTGACCTCCTCCTGTTGCAGG4065TTGAGCTCGGTCCTTCCGGACCATCACGGTGC
 GAGACACGATGTCCGACCTGCCGGAGGTGCGGAATGGAGCCTGGCACTGGAGATCCTACAACGGG
 GAGCCTCAGTCCTGGTCCAGAGGCAGCTCCGGGCGCACAGTACCAAGCCCATCCTCAGGGACCACAT
CTGTAAG4242GTAATGGCACCC₅₈TGACAGAGCGGCTCCCTCGAGGCCAGCCAGCAGCCTCGTGGG
 AACAGTCAGCCTGCCCAAGACTCAGGGAGACATGGAATCTGATCCCAGGCTCCTCCGAGTCTCA
 GCCTTGTGTGA

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATGGACACGTCCCCACACTCTTCAGG4243A4244CATGAGTGCATT
 GGTGGCTGCCGCATGGGCACA TCCCCTGGCCCCAGGGTCAGACTGGCGCGATCTGCCAACATCG
 AGGTGCGGCTCTCAGACGGCACCATGCCAGGAAGCTGGGTATACCCACCATGACAGGAAGAACGGC
 CGCAGCAGCTCTGGGCCCTCCGTGGGTCTGCTCTGCGTGGAAAG4438GTGGTCCCTGTAAGTTGTT
 TTCCCGGTGGCTGAGGGAAAGGAAGGCAGACCTGGGCCTT

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

TGACAGAGTGCCA TCTCTGC
 CTCCCAAAGCTCTAAGAGCCATGTCCCAGCCTATAUCCCATCCCACAACTGCA GCCTCATCACTGTC
 CTGTCTTCCAGC4439CGGCAAAGCCTGCGACCCCGCAGCCAGGCAGTTCAA CACCCCTCATCCCTGGT
 GCCTGCCACACCGGAACCGGCACAACCACTGGCTGGCTCTATGGAAGGCTCGAGTGGACGGC
 TTCTTCAGCACAACCGTCACCAACCCGAGCCCA TGGGCAAGCAG4605GTAGGTGGGAGGGGCATC
 CGAGGGCTGGTCAGGCTGTACTTGGCGGCTAACTAGGTGGAAGTGTGGTTAGCCAAGTGGGGA
 CAGCACCCAGGATCCCCAGGCACCTU

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36

AGACTGCTCTGCCCTCTGCCCTCCACGTCCA

CGGACAAGCTCA TAGCCAAGCCA TGGCCGTATGCTGTACAGTGCCATTCCCTCCCTGTCCCCGACG
GTGACCCGGCCTGGGTGCTACTGCCCTCGCCCACCGCGCCTCTTCCCCCAGG4606GCCCGTGCTCC
ACCCAGAGCAGCACCGTGTGGTGAACGTGCGGGAGTGTGCCCGCTCCAGGGCTTCCCTGACACCTAC
CGGCTTCTGGCAACATCCTGGCAACCACCGCAG4722GTCAAGTGGGGCGCGCTGGGCTGGAC
AGGAAGGAGGCTCTGTGCCTGTCAACCAGGTGGGCTGGGCAGCGCAGTCACI

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CAATG

CCCAGGTTGTCCTCCATCTGAGCAGGTGCTGGAGTACACCTCCCCGGCTGGGCTGGTGTCCACAT
 CAGGCATTGCCCTCTCCCTCCTGCAGG4723TGGCAATGCCGTGCCACCGCCCTGGCCAAAGCCA
 TTGGCTTGGAGATCAAGCTTGTATGTTGCCAAAGCCGAGAGAGTGCC4809GTATGGTGGGTGGGC
 CAGGCTTCCCTGGGCCCTGACTGCCCTCTGGGTACATGTGGGGCAG

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE:

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

ACTGAGCCTCTG

GGTCTAGAACCTCTGGGGACCGTTGAGGAGTGTTCAGTCTCCGTGAACGTTCCCTAGCACTCTGCCA
 CTTATTGGGTAGCTGTTAACATCAGTACGTTAATGTTCCGTATGGTCCATGTCTGTTACTCGCCTGTC
 AAGAGGGGTGACACCGGGCGTGTCCCGAGAGTGACTTTCTTTTATTCCCTT4810CAGCTAAAATA
 AAGGAGGAGGAAGCTGCTAAGGAATAGTTCTGCCCTCCCGTCACCCCTGTTCTGGCACCAGGAATCC
 CCAACATGCACTGATGTTGTTTTAACATGTCATCTGTCGGTACATGTGTGGTACATGGTGTG
 TGGCCTGGCTGACATGAAGCTGTTGAGGTCGTTATCAACTAATGATTAGTGTACAAATTG
 CAGTACTTTGTGCATTCTGGATTTAAAAGTTTTATTATGCATTATCAAATCTACCACTGTATGAGT
 GGAAATTAAGACTTATGAGTTTATGTTGTAATATTCTCAAAATACTCTCCTATAAACCA⁵¹

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

AGAACTGACT TACCTCGGAT

20

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

AGGGTGGGTC TGTGGGAGCA

20

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CAGTACACAC TAGACAGGAA

20

(2) INFORMATION FOR SEQ ID NO:42:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CACACTTACA GGTGCTGAAG

20

(2) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43

GATCTCTTAC CTCGATCTTG

20

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

CGCATCCTTA CCTCTGTCCC

20

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GGTGAGGTAA CCTCACAGAC

20

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GGCCTGACCT ACCTCCGCTC

20

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CCAAGGGTTA CCTTGACGGC

20

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

AAAGATGCAA ACCTTGCTAG

20

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TCCATGCCTC CCTTGGGTAG

20

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
- (iii) HYPOTHETICAL: NO
- (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CCAGTGCTCA CTTGAACCTTG

20

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
- (iii) HYPOTHETICAL: NO
- (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

ACACAGAAATC TGAAGGAAAC

20

(2) INFORMATION FOR SEQ ID NO:52:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

AGCTTGATGC TGCAGAGAAG

20

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

ACGGGGCACC ACCTCGAGGA

20

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

CTTGCCTTC CCTGGGGAG

20

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

ACGGCCGCTC ACCTGCTTGG

20

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TCCCGGCCTG TGGGGGAGAA

20

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GGGCCACCTA CCTGGTTATG

20

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GGGTGCCATT ACCTTACAGA

20

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

ACAGGACCCA CCTTCCACGC

20

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GCACGGGGCC CTGGGGAAA

20

(2) INFORMATION FOR SEQ ID NO: 61

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

GCCCCACTGA CTGCCGGTGC

20

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCCGGGTGGT ATGCCGTGAG

20

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CTGCTCTTAC GCTTAGCCTC

20

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GAAGGTTTCAG CTGTTTAAAG

20

(2) INFORMATION FOR SEQ ID NO: 65

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GTTGGCAGG GCTGTCACAC

20

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

CTGGCCCTAC CTGGTCTTG

20

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

CTAGCAACTC TGTCAAGCAA

20

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

TAGAGCTTTA CTTTTTCATC

20

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

GTTTGGGTGT TCTGTCACAG

20

(2) INFORMATION FOR SEQ ID NO:670:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GTTTGGCAGC TCTGCAGGGT

20

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

AGCTTGATGC TGCAGAGAAG

20

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

CAGGGGCACC ACCTCGAGGA

20

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

What is claimed is:

1. A recombinant DNA molecule comprising at least one nucleotide sequence selected from the nucleotide sequences set forth in the Sequence Listings as SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 14, SEQ ID NO 15, SEQ ID NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO 38 in a replicatable vector.

15

2. The recombinant DNA molecule according to claim 1, wherein the replicatable vector is an expression vector.

20

3. A host cell comprising the recombinant DNA molecule according to claim 2.

25

4. A method for preparing DNA methyltransferase enzyme comprising culturing the host cell according to claim 3 in an appropriate culture media, wherein the host cell produces DNA methyltransferase enzyme and separating the DNA methyltransferase enzyme from the host cell and the culture media.

5. A recombinant DNA molecule comprising a nucleotide sequence complementary to at least one nucleotide sequence selected from the nucleotide sequences set forth in the Sequence Listings as SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 14, SEQ ID NO 15, SEQ ID NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO 38 in a replicatable vector.

15 6. The recombinant DNA molecule according to claim 5, wherein the replicatable vector is an expression vector.

7. A host cell comprising the recombinant DNA molecule according to claim 6.

20 8. An oligonucleotide which inhibits DNA methyltransferase expression, the oligonucleotide having from about 8 to about 100 nucleotides and being complementary to a special target region of RNA that encodes DNA methyltransferase.

9. An oligonucleotide which inhibits DNA methyltransferase expression, the oligonucleotide having from about 8 to about 100 nucleotides and being complementary to a special target region of the nucleotide sequences set forth in 5 the Sequence Listings as SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 14, SEQ ID NO 15, SEQ ID NO 16, SEQ ID NO 17, SEQ ID NO 18, SEQ ID NO 19, SEQ ID NO 20, SEQ ID NO 21, 10 SEQ ID NO 22, SEQ ID NO 23, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26, SEQ ID NO 27, SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, and SEQ ID NO 38.

15 10. An oligonucleotide having from about 21 to about 35 nucleotides, which inhibits DNA methyltransferase expression, and comprises a nucleotide sequence selected from the group of Sequences in the Sequence Listings as SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42, SEQ ID NO 43, SEQ ID NO 44, 20 SEQ ID NO 45, SEQ ID NO 46, SEQ ID NO 47, SEQ ID NO 48, SEQ ID NO 49, SEQ ID NO 50, SEQ ID NO 51, SEQ ID NO 52, SEQ ID NO 53, SEQ ID NO 54, SEQ ID NO 55, SEQ ID NO 56, SEQ ID NO 57, SEQ ID NO 58, SEQ ID NO 59, SEQ ID NO 60, SEQ ID NO 61, SEQ ID NO 62, SEQ ID NO 63, SEQ ID NO 64, SEQ ID NO 65, SEQ ID NO 66, SEQ ID NO 67, SEQ ID NO 68, SEQ ID NO 69, and SEQ ID NO 70.

30 11. An oligonucleotide having from about 13 to about 19 nucleotides, which inhibits DNA methyltransferase expression, and comprises a nucleotide sequence selected from the group of Sequences in the Sequence Listings as SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42, SEQ ID NO 43, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO 46, SEQ ID NO 47, SEQ ID NO 48, SEQ ID NO 49, SEQ ID NO 50, SEQ ID NO 51, SEQ ID NO 52, SEQ ID NO 53, SEQ ID NO 54, SEQ ID NO 55, SEQ ID NO 56, SEQ ID NO 57, SEQ ID NO 58, SEQ ID NO 59, SEQ ID NO 60, SEQ ID NO 61, SEQ ID NO 62,

SEQ ID NO 63, SEQ ID NO 64, SEQ ID NO 65, SEQ ID NO 66, SEQ ID NO 67, SEQ ID NO 68, SEQ ID NO 69, and SEQ ID NO 70.

12. The oligonucleotide according to claim 8, wherein
5 the oligonucleotide has at least one internucleotide linkage
selected from the group consisting of phosphorothioate,
phosphorodithioate, alkylphosphonate, alkylphosphonothioate,
phosphotriester, phosphoramidate, siloxane, carbonate,
carboxymethylene, acetamide, carbamate, thioether, bridged
10 phosphoramidate, bridged methylene phosphonate, bridged
phosphorothioate and sulfone internucleotide linkages.

13. The oligonucleotide according to claim 12, wherein
15 the oligonucleotide is a chimeric oligonucleotide comprising a
phosphorothioate, phosphodiester or phosphorodithioate region
and an alkylphosphonate or alkylphosphonothioate region.

14. The oligonucleotide according to claim 13, wherein
the oligonucleotide comprises a ribonucleotide or 2'-O-
20 substituted ribonucleotide region and a deoxyribonucleotide
region.

15. A method for inhibiting tumor growth in a mammal,
including a human, comprising administering to the mammal,
25 which has at least one tumor cell present in its body, a
therapeutically effective amount of an antisense
oligonucleotide according to claim 8 for a therapeutically
effective period of time.

30 16. The method of claim 15, wherein the mammal is
administered a therapeutically effective amount of more than
one antisense oligonucleotide according to claim 9 for a
therapeutically effective period of time.

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THE - 1 (cont.)

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TTCCCAGGCAAACCTGGCAGTTACATTAGGAATGACTAGCTAGAGACATCCCTGAAGAATGAGT
TATTGGGGGCCACGCCCTTAACCTCACCTCTTAACCTCACCTCTTATCTGCCCTCTGTGGTACCCCTTGCT
TCCCTGGATGCTTGACTCCCCCATTTCAATCCTCAAATGCCACCCCCCACAGGCCCTTAGGAACCA
TCAGCTGGCTTCCCCACAGTGTCTGGCCCTGGCTACTCATTCAGACACTGGCCATACTGTGGC
ACACCTGGTATGGGCTGTGTCAGACCCAACTGGAGAAAGACCAAGCTGTAGGTCAATTCCCTTACGG
GAGTGGCCCAACTATATGACCTGGCCCTCTTCTGGTATCTTGTAGTCAGGGTCTCACTCTGTCT
CCTAGATTGGAGTGCAGTGATGCAAATCACGGCTCACTGTGGCCTCGACCTCCAGGGCTCAGGTGATCT
TCTTCAGGCTCCCAAGTAACCTGGACCAACAGCACATGCCACCAACCCAGTTATTTTATT
TTATTTTATTTTATTTGAGACAGAGTTCACTCTGGCTTCAAGTGAATTGGCTAGAGTGCAATGGTGTGACCA
GCTCACTGCAACCTCTGGCTTCAAGTGAATTGGCTCAGGCTCCAAAGTGTGGGATTAC
AGCCACCCACCCACGGCTGGCTAATTGGTATTAGTAGAGATGGGGTTGCCATGGTGGC
CAGGCTGGTCTCAAACCCCTTGACCTCAGGTAATCCACCCACCTGGCCCTCAGGTAATCCACCCAACT
GCTGCTGATGTTGGATTCCAGGCATCAGGCCACCCAGCCACTAATTGGTATTGTTGTAGA
GATGGAGTTGCCATGTTCCAGGCTGGCTGTAACCCCTGGCTCAAGTGATCCGCTCGCCTTGCG
CTCCCAAAGAGCTGGATTATAAGCGTGAGCCACCATGCCCTGGTACCTTAAATATAACA
GGCTGGGCATGATGGCTCATGCCCTGTAATTCCCAGGCACTTGGGAGGGCTGAGGCAGGGATCGCCTG
AGGTGGGAGTTGAAACCTAGCCTGACCAACACGGAGAAACCCCTGCTAAAAATATAAAAT
TAGCTGGGTGATGGTGGCATGCCCTGTAATCCAGCTACTCGGGAGGCTGAGCCAGGAGAATCGCCT
GAACCTGGGAGTCCGGAGGTTGAGGATCACACCAATTGGCAACTCCAGGCTGGGCAACAGAGCAA

7 - 1 (cont.)

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GTTGTTTGTGAGACAGAGCTCACTCTGTCAACCCAGGCTAGAGTCACGCCGGATTCAGCTGTTCTGCCTCAGCCTCCCAAGTAGCTGGAC
GCCTCACTGTGACCTCTGGCTCCGGATTCAGCTGTTCTGCCTCAGCCTCCCAAGTAGCTGGAC
TACAGGCACCCAGCTGGCTCCGGATTCAGCTGTTCTGCCTCAGCCTCCCAAGTAGCTGGAC
CCAGACTGGTCTTGAACCCGGCTGGCTGGATTCAGCTGTTCTGCCTCAGCCTCCCAAGTAGCTGGAC
CGTGACGACCATGGCTGGCCAGGTTTAACTACCAATCTCAGTTCTAAACAACCTCTACTC
TGGATTGTAACCTGTCCCTGGTAACACTGTTTATTGTGTTTGTGAGATAGGGCTCTC
ATTCTGTAGGCCAGGCTGGCAGTGGCAGTGGCTCAACTACAGGCTCAACTGCAACCTCGCCTCCAGGCTC
AAGTGATTTCACCTCAGCCTCTAAGGACAAATTGGCTCATGGTCAAGCCACCATGCCCCAGGCTGGCTTGAACCTGGGGCT
TTTAATAATTGTAAAGATGGGATTGGGATTTGTCATGGTCAAGCCACCATGCCCCAGGCTGGCTTGAACCTGGGGCT
CAAAGCAATTCCACCTGGCTCCCAAGTGCTGGATTATAGGTGTTGAGCCACTGTGCTGGGC
CGACACTTACAGAACAGTATTCTTATAACCATTGATATGTCCTCCATCTCACCTCCAGCTTTC
CCATTTCACCACTTGGAGACAGGGAGTGAAGTGATCCTAATGGAAATTCCCTGAACACATTCACTG
ACTGTTAGGTGTTTGACTGAGACAGCATTGCCATTCACTCATGGTGAATGTGATCAGGCAGGCTC
AATAATTGTGTTATTAGTCCACTAGTGAATAGCTTGGGAATGTGGGTACTGCTAAACCTATATCCCTTC
CCTAGG115AATTGAGAGAAATTGAATCTGCAAGAATTTCCTGGAG222GTAA
AAAGAAATTCAAGTAAACCAAAATTACGTAAGAAGAATTATCCGAG222GTAA
GTCAAGTTCTCAGCATTCCCTAGCCTCTAGAAAAATTGCTCTCCCTAGTAACCTGTCCTGACCCAGGAGG
CAGCAAGATCCCCAGCTGCCTCATGGCTGATGATGATGATGATGATGATGAAACACA
TGTGTTCTGACACCGTTACATTCACTGCTACTAATTATCCCTGCTTGTGACCCAGGAGG

THEORY - 1 (cont.)

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CTACCTGGCTAAAGTCAAATCCCTGTTAATAAAGATTTCGCTTGAGAACGGTGCTCATG
 CTTACAACCGGAAAGTGAATGGACGTCTAGAAACCGGGAACCAAGCAAGAACGGCG
 TAGAGTGGGAATGGCAGATGCCAACAGCCCCAAACCCCTTCCAAACCTCGCACGCC
 AGGAGGAGCAAGTCCGATGGAGGGCTAAGC442
^{0160 63} GTAAAGAGCAGATGATTCCTTATTTTAA
 TTGTTTTGAGATGGAGTCTCACTGTGTTGCCAGTGTGAGGCACAGTGTAAACCTCGGCTCACTG
^{Seq. ID. No. 4} ^{0160 64} ⁵ TAACCCCTCTGCCTCCAGGTTCAAGAGACCCCTCAGCCTCAGGCTTCAAGTAACCTG
^{Seq. ID. No. 5} AACATTAGCAAGCTGGTTGACTAGAATAAAATGCAAAGATGCTAGTCCCTAGAACCTGGCTT
 CCTGCAATAGCTTAGTAATGTTGAACTGCAATTATGCTGTGGGCTTCTATTGATAAGTGGCTTTTT
 TTTCTTTATGCTTTCTTAAACAGC443
^{0160 64} TGAACCTTCACCTAGCCCCAGGATTACAAG
 GAAAAGCACCAGGCAAACCAACCACATCACATCATTGCAAAGGG518GTCAAGTATACGATAA
 ATTGGCGGGCTGCCTTTAGGGGGGGCTGTTTGGGATGGAAATTGGTAGGGCGTCACGTGGCAATT
^{Seq. ID. No. 6} ^{0160 65} CTGCTTCCGGTTGTATA1000bp-nnnfCTGACACTAGCAGCTGTTGATCGGGTGTAGACCC
 GTGATTCTAGGACTTACAAGATGGCAAGACAAACATTCTAAACCCGTCAATTCAAGAAACATTAAA
 CTTGAAGCCTCTTCAACATCCCTGGTGAATGAGGGTCCACTTCAGGCCAGCTGGAGGGCTAGGGTCTT
 GTCCTCAACTAATGGTTGGCCTCACTGTGTGACAGC519
^{0160 66} GTCTGAAAGAGCCAAATCGGATGAGTCCCATCAAG597GTAGGGC
 CAGTGCTTCATTCCTGACTCTACCTTACTGGTGTATTGACTATGTTGTTCTGT
 CCAAGTAAATAAAACCCCTGTCTAGGGCTCTATTAGGGCTCTCCAGAGACAGGACCAATAAGAAT
^{Seq. ID. No. 7} ^{0160 67} GTATATGTTGTATCAACCGTATA1500bp-nnnGTTGGGGTGGGATTAAATACCAAGAGT

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THE - 1 (cont.)

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T H E — T (cont.)

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TCGACACGGGCTCATCGAGAAGAATATCGGAACTCTTCTGGTTCAAGCAAAACCAATC
 TATGATGATGACCCCGTCTTGTGAAG 1348 GTAAAGGAATAGTCCGGATTATGTTGGGACACCTT
 TAAAACAGCCAGGGCAAGGTTGGCTCACATCTGT^{SEQ. ID. NO. 16} TAATCCTAGCACITGGGGCTGAGGCCAGAGGAT
 CACTTGAGCCCCGGAGTTnn~450bp~nnTTTAGTCCATTTCCTTCTGCTTAGG 1349 TGGTGT
 AATGGCAAAATCTTGGCCCCATAAATGAAATGGTGGATCACTGGCTTGTGAGGTGAAA
 AGGCCCTCATCGGCTTCAGCACCT 1441 GTAAAGTGTGTGGCCATCATAGGCTGGGGTCTGA
 AAGGGGCCATGGTCTCCTCCCTGGGGCTGACGGGCTCTGGTGGGAATTCAGCAGGCCCTTGC^{SEQ. ID. NO. 17}
 GAAGGGCCAT TGTGACTTGGGAACCTTAGCAGGGTTCAAGTGGGTAGATCTCTGTGTTAGTTAGGnn
 ~900bp~nnCCGCTCTGGCTCAGACAGGCTTCTCAGAACAAAGCCAGCTATGATGTGTGTGCC
 TATGTTCTGACATTGGGTACGGGATGAACTTTAGACTGTTGGGTGAGTTGGTAGACTCCCTCCARTG
 CCTGTGGCCACTGTAGGGCCATCAGATTCCAGGGCCATTCACACCTCCTCTGGCCCCAGC 14
 42 ATTGGCCAAATACATCTGATGGATCCCAAGTCCCGAGTATGGCCCATATTGGGCTGAT
 GCAGGAGAAGATCTACATCAGCAAGATTGTGGAGTTCCCTGCAGAGCAATTCCGACTCG
 ACCTATGAGGGACCTGATCAACAAAGATTCGAG 1593 GTAAAGAGATCCAGGGTCCCTCAGCATCCGGGA
 TTCCCACTGGAAACTTGCCCTCAGAACCAAGCAGACACTGTTCTTCAGTTGGATTAGGCCAGTTGGC
 TTAAGGCATGAGAGAAACCTGTTCTCAAGA 1594 CCACGGGTTCCCTCAGTTGGATTCTGCCCTCAACTTG
 AACCGCTTCAAGAGGACTCCCTCCCTGGCACAGGGCAGTTGTGGAGCAGGGTGGAGA
 GTTATGACGGAGGGGGACAGTGATGAGCAGCCCCATCTTCCTGACGCCCTGCAATGCCGGGA
 CCTGATCAAGCTGGGTCA CGCAGAG 1781 GTAAAGGATTCGGGCTGGGACCAAGAG
 OLIGO 44

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~~7~~ ~~1~~

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TGAAGACTGGAGACGGGGAGGGTAGAGGCATGGCCCACATCCCTCTGTCCCCAGTCCTCTGAGATGCTG
 GAACCTCTCCCGTAGG1782CGAGCCCAGGGCAGGGCAGACCATCAGGCATTCAGGCATTCAGGG
 AGAAGGA CAGGGGACCCACGAAAGCCACCAAGCTGGTCTACAGATCTTCGATAC
 TTTCTCGCAGAGCAAATTGAAAGGATGACAGAGAAAGACAAGGAGAACGGCTTAAAGCG
 CCGCGATGTGGCTCTGTGAG1968GTAACCTCACCTGTGGCTGAGTGGGTGCTCCCCCTAAGGGTGGC
 CCAGCCTCTGGCCTGATCTGAGGGACTGCTCCATCTCTCTGTGGCTTGTGAGACTCTGGCTGCTCAAATG
 SEQ. ID. No. 18 $\xrightarrow{\text{Seq. ID. No. 19}}$ SEQ. ID. No. 19
 TGACCCCTGAGACAGAAATTGTTGTGGmnmCTGTGGCCAGGCTCTGTTGCCTTTTAGG
 1969 TGTGTCAGCAGCCTGAGTGTGGAAATTGTAAGGCCCTGCAAGGACATGGTTAAATTGG
 TGGCAGTGGACGGAGCAAGCAGGCTTGCCAAAGGAGCGGAG2066GTAGGGTCAGGCCAGTCTCC
 TCCTGTGGCAGAGGACTTGCCAGCTGGCAGATGCCACTGTGGAGAAGGGCCGTCAATGTGTGGGAC
 SEQ. ID. No. 20 $\xrightarrow{\text{Seq. ID. No. 19}}$ SEQ. ID. No. 20
 AGCACCAGGATTCCCTCGmnm~180bp~nnAGACCTGTCCCCCTGTTATGAAAGAAAACAGCCCCGGTTGGCT
 TACTTAGAAAAGGGCCCTTAGGTATAACCAGTGACATTGCAAGG2067TGTCCCAATATGCCATG
 AGGAGGCAGATGACGATGAGGAAGTCGATGATAACATCCCAGAGATGCCGTACCCAAA
 AAATGCAACAGGGAAAGAAGAAAGAACAGAACAGAAATCGCATCTTGGGTGCGGAGAAG
 CCGTCAAG2214GTAACCCCTGGAGTCCCCCTGGTCACTGCmnm~1500bp~nnAAGTCAAGG
 SEQ. ID. No. 21 $\xrightarrow{\text{Seq. ID. No. 22}}$ SEQ. ID. No. 22
 CCAGCAAAGACCCCTCAGAATGATCCCTCATGAACCTATGCTCTCATTTCAAGA2215CTGATGGGAA
 GAAGAGTTACTATAAGAAGGTGTGCATTGATGCCAGATTCCTAGCAAG2330GTTGGCATCTTCTT
 CTCTGTTATTCCAGATGATTCTCAAAACCGCTGTATCTAGCAAG2330GTTGGCATCTTCTT
 TTGGCTTGACTTCTGCACCTCTCATCAAGTAGGAGAATGCCCTGmnm~150bp~nnCTCCCAGTGCC

7 2 2 - 1 (cont.)

12/22

CGTCTTCTATTCCAGG2331GTCACGGCGCTGGAGGACAGCAGCAACGGGAGATGTTTC
 ACGCCCCACTGGTTCTCGCGTGGACAGACACAGTCCCTCGGGCACGGTCCCTCTGGAA
 GCTGTTCTGGGATGAAATGTCAGGACATGCAGACTGGCCATGGAG2535GTCAGGCTGGTCTCGT
 SEQ. ID. NO. 24 ^{SEQ. ID. NO. 25} GAGCCCh400bp~mGACCCAAAGCCCCCTCCGAAACTGGGCAATCTTGTGAGTCTCCCAAGG2536GAGGCATGGATCCCG
 AGTCCCTGCTGGAGGGGACGACGGAAAGACCTACTTCTACCAAGCTGTGGTATGATCAAGA
 CTACCGGAGATTCGAGTCCCTCCAAAAACCCAGCCAAACAGAGGACAACAAGTCAA2669G
 TGAGCAGTGGGGCTGGACTCGGGGTCAAGCAGGCACTTTCAGCCCCACATCACTCCCTCACCGGCTGTC
 SEQ. ID. NO. 25 ^{SEQ. ID. NO. 26} TGCCGm~850bp~mAGCTGGCAAGTAGCTGCTGCCCACTGCGGGCAACTGCCCTCAGGGCCTATGTTTC
 TGTCCTTGTTCCTTCAGA2670TTCTGTGTGAGCTGGCTGCCGTCTGGCTGAGATGAGGCAA
 AAGAAATCCCCAGGGTCCCTGGAGCAGCTCGAGGACCTGGATAGCCGGGTCTACTACTC
 AGCCACCAAGAACGGCATCCTGTACCGAGTTGGTGAATGGTGTACCTGCCCTGAGGCC
 TTACACGTTCAA2843GTAAGTGGCCCCCTCGGAGCAGGGCCAGGGGm~450bp~mAAATCATTT
 CTTAGGGTACACACCTACCTTAATTCACTCAGGTGCTTGACTTAAATGGTTATTTCAC TGCTGAGTC
 ATGCCCTGACTGACCAACTGCCAAGGGTGAAGGTCAAGTGGGTGCTTCTGCAGGC2844A
 TCAAGCTGTCCAGTCCCGTGAACAGCCCCACGGAAAGGAGCCGGTGGATGAGGA
 AGGGCACTACGGAAATACTCCGACTACATCAAAGGCAGCAACCTGGATGCCCTGAGGCC
 TACCGAATTGGCCGGATCAAAGAGATCTTCTGTGTCAGGCAAGAGCAACGGCAGGCCAATG
 AGACTGACATCAAACAGTTCTACAG3065GTCAGCAGGGCTCTGTCTCTCC

7 1 (cont.)

/3/22

SEQ. ID. NO. 27 \rightarrow SEQ. ID. NO. 28
 TCGAGGCCACAGACTCTAGAAGGGCTCTGCTGAAACAAAGGTTGGnn~520bp~mnAAAAGGAGAG
 CTCCTAACCGAGGCCACTCCGGCTCGCAGG 3066CCTGAGAACACCCACAAGTCCACTCCAGCGGA
 GCTACCAACCGAGACATCAACCTGCTCTACTGGAGCGAGGAGGGCCGCTGGACTCTCAA
 GGCTGTGCAGGGCCGCTGCACCGTGGAGTATGGGGAGGCCTGCCCGAGTGCCTCAGGTG
 TACTCCATGGGGCCCAACCGCTCTACTCCCTCGAG 3258GTGGTGGCTGGCTAGAG
⁰¹⁶⁰₃₃ GGAAGGCTTCAGGGTCAAAGTTGGCCAGAAGGGAGTCTGATGTCCGGGTTATACACAAGGGGCTTGCG
 TGGAGGGTTTCAGCTTTGTAAAGAAGTGGGTGGTGGCTGACGTTGAAAGCTGTTCTGCAGGGAGCTTAC
²⁸₂₉ SEQ. ID. NO. 28 \rightarrow SEQ. ID. NO. 29
 GGGGGnn~950bp~mnGTCAACTACTCTATTGGTGGCTAATTGGTCATGGCCCACTGAGGGAGAATTAA
 GTGACTATCAATTGGCCTTACTAGTCTGCGTTAGAGGGGACAGTGGCGTTCTCCAAACGA
 TTGCAGTTCTCCTTCAGG 3259CCTATAATGCAAAGGCAAGGGAAAAG 3343GTACGTCATTGTAT
 ACCATGCCGTAGCCCTGGAAACAAAGGGAAAGGGCAAGGGAAAAG
 GAGTTCTCAAGTTCTCTCTGTAACCTGGAGGGCTGCCTGTGAATCCCTCAGTGTAAAACC
 TCTGGTGTACTGACTCTGGACAGCGAGGGCCGCTGAGTTAACAGGGCTTGAGAGCAAGGTGGA
 CTTGGACTCTGAGGATCGGGTTAGCCCTCTGGCCTCTCCCCAGG 3344GAAGGGCAAGGCCAAG
⁰¹⁶⁰₃₄ TCCAAGGCCTGTGAGCCAGGCCAGAGATAAGAGATCAAGCTGCGGCC
 TGGATGTTCTGGCTGCCGGGGTTGTCGGAGGGATTCCACCAAGCAG 3472GTGAGCGC
⁰¹⁶⁰₃₅ CCGTAGGGCTCCATCTCTGAATACTGGTGAAGCCAGAGGGCAGGGCTACCTGAAACGACTTCCAA
²⁹₃₀ SEQ. ID. NO. 29 \rightarrow SEQ. ID. NO. 30
 CCCGGTCAACCTTCTGATCTAAGAATCTCTGGAGAGTGAAGCAGGCT
 GGGTGAAGAGGAGACTCCATCTCAAAAAAAATCTTCTGGAGAGTGAAGCAGGCT

789 - 1 (cont.)

14122

TCGTGCTTGAATCTGCCAGG3473CATCTCTGACACGGCTGTGGCCATCGAGATGTGGGACCCCTG
 CGGCCAGGGCGTTCCGGCTGAACAAACCCGGCTCCACAGTGTTCACAGAGGACTGCAACAT
 CCTGCTGAAGCTGGTCATGGCTGGGAGACCAACTCCCCGGCCAGGGCTGCCAGGGCTGCCAG
 AAGGGAGACGTGGAGATGCTGTGGGGAGACCCACTCAAGTCAAAACTCTCTGGTGGTTCCCTCAGGGCATGAAACC
 GCTTCAATTTCGGCAGCTTCAAGTCCAAAGTCAAAACTCTCTGGTGGTTCCCTCAGGGCATGAAACC
 TAAACGGGTAGAAGCCCCCCCAGTGTGCCAGACGGCCGGGGCTGTGGCATGTGAGCTGCAATT
^{SEQ. ID. NO. 31} ³⁰ ³¹ ³² ³³ ³⁴ ³⁵ ³⁶ ³⁷ ³⁸ ³⁹ ⁴⁰ ⁴¹ ⁴² ⁴³ ⁴⁴ ⁴⁵ ⁴⁶ ⁴⁷ ⁴⁸ ⁴⁹ ⁵⁰ ⁵¹ ⁵² ⁵³ ⁵⁴ ⁵⁵ ⁵⁶ ⁵⁷ ⁵⁸ ⁵⁹ ⁶⁰ ⁶¹ ⁶² ⁶³ ⁶⁴ ⁶⁵ ⁶⁶ ⁶⁷ ⁶⁸ ⁶⁹ ⁷⁰ ⁷¹ ⁷² ⁷³ ⁷⁴ ⁷⁵ ⁷⁶ ⁷⁷ ⁷⁸ ⁷⁹ ⁸⁰ ⁸¹ ⁸² ⁸³ ⁸⁴ ⁸⁵ ⁸⁶ ⁸⁷ ⁸⁸ ⁸⁹ ⁹⁰ ⁹¹ ⁹² ⁹³ ⁹⁴ ⁹⁵ ⁹⁶ ⁹⁷ ⁹⁸ ⁹⁹ ¹⁰⁰ ¹⁰¹ ¹⁰² ¹⁰³ ¹⁰⁴ ¹⁰⁵ ¹⁰⁶ ¹⁰⁷ ¹⁰⁸ ¹⁰⁹ ¹¹⁰ ¹¹¹ ¹¹² ¹¹³ ¹¹⁴ ¹¹⁵ ¹¹⁶ ¹¹⁷ ¹¹⁸ ¹¹⁹ ¹²⁰ ¹²¹ ¹²² ¹²³ ¹²⁴ ¹²⁵ ¹²⁶ ¹²⁷ ¹²⁸ ¹²⁹ ¹³⁰ ¹³¹ ¹³² ¹³³ ¹³⁴ ¹³⁵ ¹³⁶ ¹³⁷ ¹³⁸ ¹³⁹ ¹⁴⁰ ¹⁴¹ ¹⁴² ¹⁴³ ¹⁴⁴ ¹⁴⁵ ¹⁴⁶ ¹⁴⁷ ¹⁴⁸ ¹⁴⁹ ¹⁵⁰ ¹⁵¹ ¹⁵² ¹⁵³ ¹⁵⁴ ¹⁵⁵ ¹⁵⁶ ¹⁵⁷ ¹⁵⁸ ¹⁵⁹ ¹⁶⁰ ¹⁶¹ ¹⁶² ¹⁶³ ¹⁶⁴ ¹⁶⁵ ¹⁶⁶ ¹⁶⁷ ¹⁶⁸ ¹⁶⁹ ¹⁷⁰ ¹⁷¹ ¹⁷² ¹⁷³ ¹⁷⁴ ¹⁷⁵ ¹⁷⁶ ¹⁷⁷ ¹⁷⁸ ¹⁷⁹ ¹⁸⁰ ¹⁸¹ ¹⁸² ¹⁸³ ¹⁸⁴ ¹⁸⁵ ¹⁸⁶ ¹⁸⁷ ¹⁸⁸ ¹⁸⁹ ¹⁹⁰ ¹⁹¹ ¹⁹² ¹⁹³ ¹⁹⁴ ¹⁹⁵ ¹⁹⁶ ¹⁹⁷ ¹⁹⁸ ¹⁹⁹ ²⁰⁰ ²⁰¹ ²⁰² ²⁰³ ²⁰⁴ ²⁰⁵ ²⁰⁶ ²⁰⁷ ²⁰⁸ ²⁰⁹ ²¹⁰ ²¹¹ ²¹² ²¹³ ²¹⁴ ²¹⁵ ²¹⁶ ²¹⁷ ²¹⁸ ²¹⁹ ²²⁰ ²²¹ ²²² ²²³ ²²⁴ ²²⁵ ²²⁶ ²²⁷ ²²⁸ ²²⁹ ²³⁰ ²³¹ ²³² ²³³ ²³⁴ ²³⁵ ²³⁶ ²³⁷ ²³⁸ ²³⁹ ²⁴⁰ ²⁴¹ ²⁴² ²⁴³ ²⁴⁴ ²⁴⁵ ²⁴⁶ ²⁴⁷ ²⁴⁸ ²⁴⁹ ²⁵⁰ ²⁵¹ ²⁵² ²⁵³ ²⁵⁴ ²⁵⁵ ²⁵⁶ ²⁵⁷ ²⁵⁸ ²⁵⁹ ²⁶⁰ ²⁶¹ ²⁶² ²⁶³ ²⁶⁴ ²⁶⁵ ²⁶⁶ ²⁶⁷ ²⁶⁸ ²⁶⁹ ²⁷⁰ ²⁷¹ ²⁷² ²⁷³ ²⁷⁴ ²⁷⁵ ²⁷⁶ ²⁷⁷ ²⁷⁸ ²⁷⁹ ²⁸⁰ ²⁸¹ ²⁸² ²⁸³ ²⁸⁴ ²⁸⁵ ²⁸⁶ ²⁸⁷ ²⁸⁸ ²⁸⁹ ²⁹⁰ ²⁹¹ ²⁹² ²⁹³ ²⁹⁴ 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SUBSTITUTE SHEET (RULE 26)

16/22

TTTCCCTCCCTGTCCCCGACGGTGAACCGGGCTGGGTACTGCCCTCGCCACCCGCCCTCTTCCC
 CCAGGG4606^{SEQ. ID. No. 60} GCCGGCTGGCTCCACCCAGGCACCGTGTGGAGCTGGAGTGTGCC
 CGCTCCCAGGGCTTCCCTGACACCCTACCGGGCTCTCGGCAACATCCTGGACAAGCACCGGCA
G4722^{SEQ. ID. No. 61} GTCAGTGGGGCGCGCTGGACAGGAAGGGGGTCTGTGCCCTGTCACCAGGTGG
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17/22

Western blot analysis of U1, U2, and U4 snRNPs. The blot shows bands for U1, U2, and U4 snRNPs across four lanes: C, U, I, and U. A 190kDa marker is indicated on the right. A legend on the left shows SAM: - - + + and Boiling: - + - +.

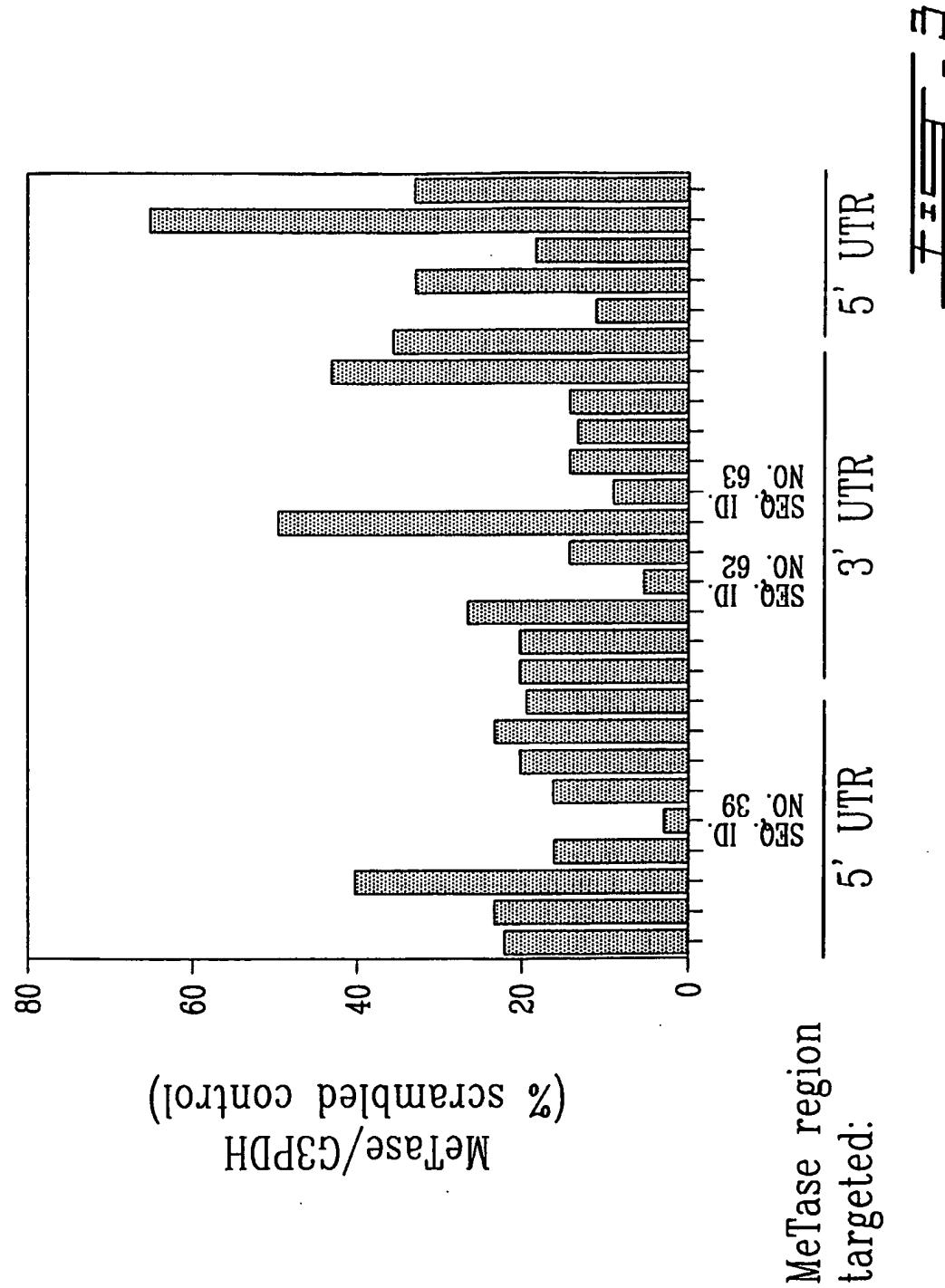
Conditions:

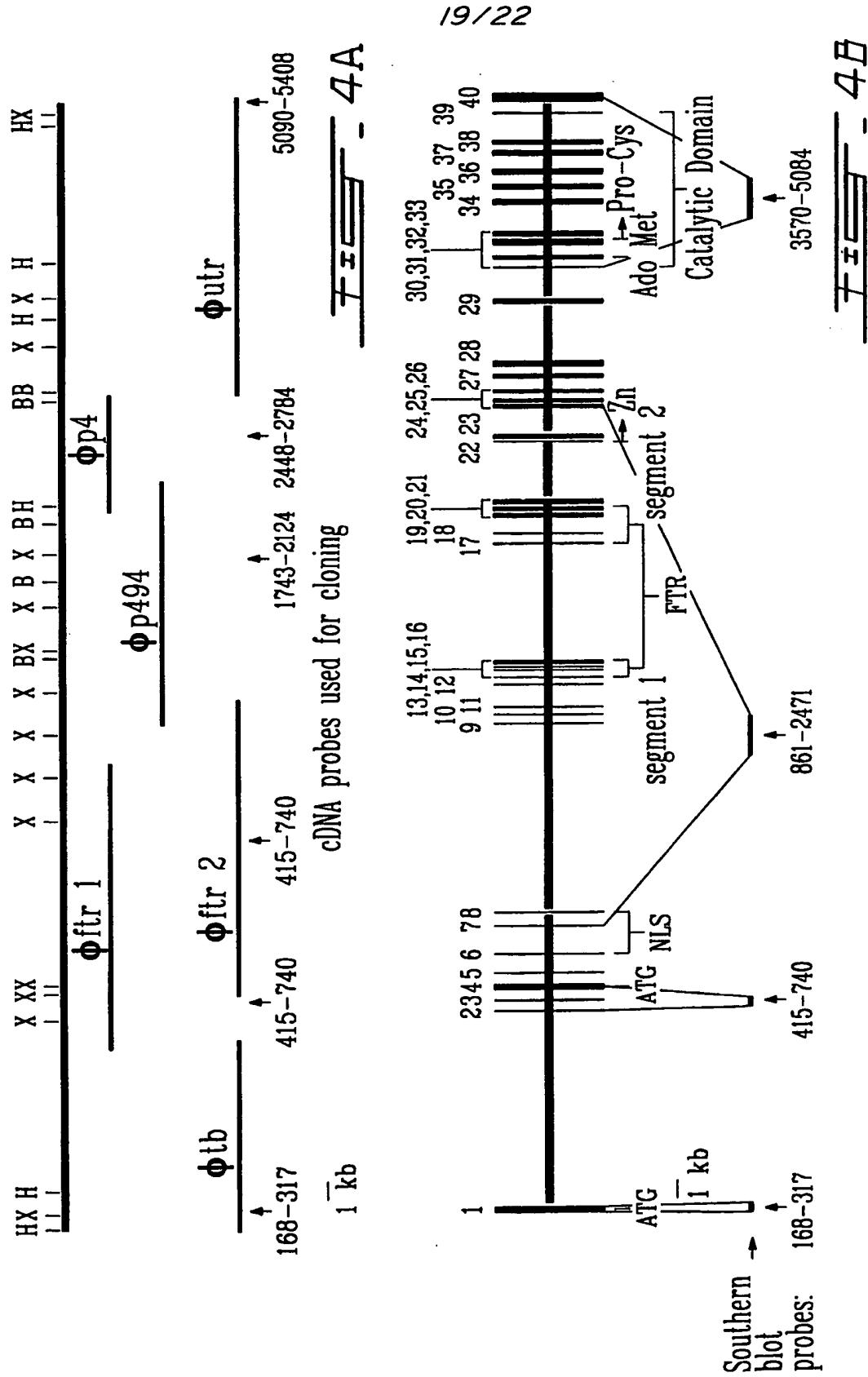
Boiled prior to PAGE

**Western blot reacted
with an α DNA McTase
antisera**

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18/22



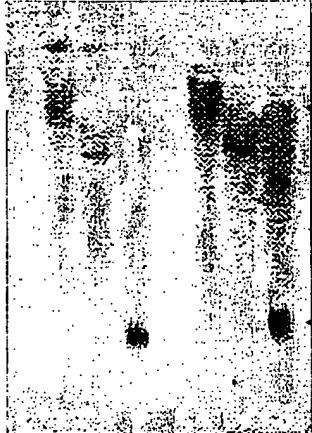


20/22

probe: 168-317
(exon 1)

T 24 A 549

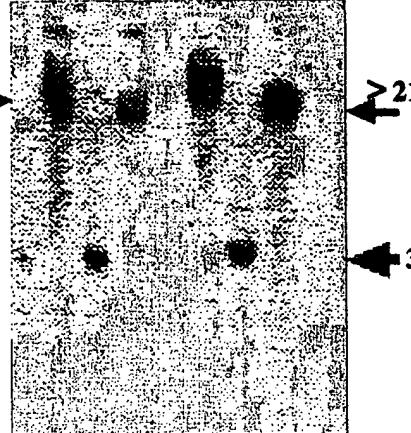
B X H B X H



probe: 415-740
(exons 3-5)

T 24 A 549

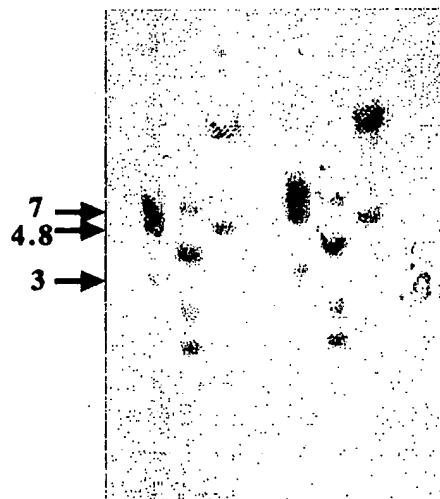
B X H B X H



probe: 861-2471
(exon 7-24)

T 24 A 549

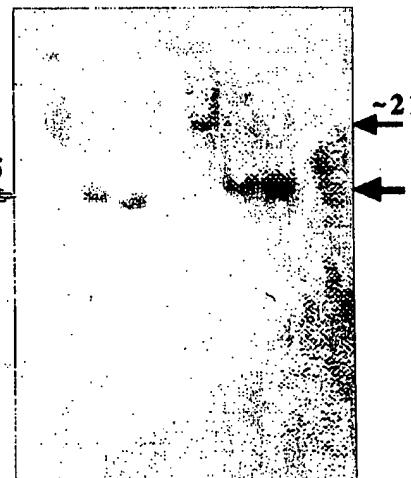
B X H B X H



probe: 3570-5084
(exon 30-40)

T 24 A 549

B X H B X H



← Bam H1

↔ Xba 1

← Hind III

 - 4C

3' intron--5' exon.....3' exon--5' intron

Exons cdDNA location

	1-317	→ initiation codon	CGT.....GCGgttaggttaccatgg
1	318-354		cctatttttcctccaggGCT.....AAGgttaatctccctttaaa
2	355-462	→ initiation codon	ctataccctcccttagGAA.....GAGgttaagtcaagtttctcg
3	463-682		tcctgttcgtctgttagGAG.....AGCgttaagagcagatgatt
4	683-758		tttttttttttaaacaggCTG.....GGGgtcagtagatacgataaat
5	759-837		cactgtgtgtgacagCCC.....CAGgttagggccaggctttc
6	838-872		ccttcctccacacagGAT.....ACGgttaagaatagttactat
7	873-957	NLS	gttatttttgcgttgacagAGT.....AAAGgttaaagctctatcacc
8	958-992		tttccctgtcaacttagGAA.....ACCGgttaagtgcagcgaacc
9	993-1080		ttgtcttctgtgacagAAC.....AAAGt
10	1081-1115		cctttttttctgtcagGAT.....TCTgtcaagtgtttaaaatgt
11	1116-1197		tctgttaccctgcagAGC.....AAGgttaagggtctcacttttc
12	1198-1232		ttgtttccctgtgttagGAG.....ACCgttaagaattttattcttga
13	1233-1278		gattttttttcccaagAAC.....AAGgttaaaggatctgcgggg
14	1279-1359		ttcctgtccacagACC.....GCGgttcgtacagctctttcc
15	1360-1469	FTR	cccggtgttcgttagGTG.....CAGgttaagtgcacatttcgtgt
16	1470-1588		tttgtttccctgtctagTGT.....AAGgttaaggaaatagtccgg
17	1589-1681		tcctttttctgtcttagGTG.....CCTgttaagtgttgcccat
18	1682-1833		ctctgttcgecccaagCAT.....GAGgttaagagatcgggttc
19	1834-2021		cctgttctctttcaagACC.....GAGgttaaggatgcggctggg

21	2022-2208	Zn
22	2209-2306	
23	2307-2454	
24	2455-2570	
25	2571-2775	
26	2776-2909	
27	2910-3083	
28	3084-3305	
29	3306-3498	
30	3499-3583	
31	3584-3712	—AdoM
32	3713-3995	—Pro-C
33	3996-4137	VII
34	4138-4304	VIII
35	4305-4482	
36	4483-4678	
37	4679-4845	
38	4846-4962	IX
39	4963-5049	X
40	5050-5409	

Catalytic Domain

gaacctcccgtagGCG.....GAGgtaaccccacctgtggg
tttttatgccttttagGTG.....GAGgtaggccaggccgagt
ccagtgcattcgagGTG.....AAGgtaaacccttggagtc
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ccgtcttctattcccgGGT.....GAGgtgagttgcctgtgtcc
ctttgagttcccaagGGA.....CAAGttagactggggctg
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THESE = 5 (cont.)